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CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

Anti-PD-1 and Anti-PD-L1 Monoclonal Antibodies in People Living with HIV and Cancer

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Abstract

Purpose of Review Immune checkpoint inhibitors targeting the programmed cell death-1 (PD-1) pathway are a class of anti-cancer immunotherapy agents changing treatment paradigms of many cancers that occur at higher rates in people living with HIV (PLWH) than in the general population. However, PLWH have been excluded from most of the initial clinical trials with these agents.

Recent Findings Two recent prospective studies of anti-PD-1 agents, along with observational studies and a meta-analysis, have demonstrated acceptable safety in PLWH. Preliminary evidence indicates activity in a range of tumors and across $CD4^+$ T cell counts.

Summary Safety and preliminary activity data suggest monoclonal antibodies targeting PD-1 or its ligand, PD-L1, are generally appropriate for PLWH and cancers for which there are FDA-approved indications. Ongoing and future trials of anti-PD-1 and anti-PD-L1 therapy alone or in combination for HIV-associated cancers may further improve outcomes for this underserved population.

Keywords PD-1 · PD-L1 · Checkpoint inhibitors · HIV · Cancer · T cell exhaustion

Introduction

People living with HIV (PLWH) who start antiretroviral therapy (ART) and maintain a suppressed HIV viral load can now experience a life expectancy close to that of the general population, especially if ART is started before profound immunosuppression [1]. Despite progress in HIV care, cancer remains one of the most common causes of morbidity and mortality among PLWH worldwide [2•, 3]. People with uncontrolled HIV and low $CD4^+$ T cell counts remain at particularly high risk for Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer. There was a significant decrease in the incidence of these cancers after the widespread introduction of combination ART in 1996 [4]. However, even with excellent viral control and immune reconstitution, PLWH remain at increased risk for a range of cancers, especially lung cancer and those driven by oncogenic viruses [5]. Also, as PLWH live longer, they remain at risk for these cancers for a longer period of time. Thus, the burden of cancer in PLWH globally is anticipated to grow given decreased mortality from infectious complications of HIV and an aging of the population [2•, 5, 6].

Among the most effective novel agents that have gained widespread use across cancer subtypes in the last decade are the programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors. These agents have drastically changed the treatment paradigm for many cancers, including melanoma, non-small cell lung cancer (NSCLC), and Hodgkin lymphoma [7–9]. There are currently three Food and Drug Administration (FDA)–approved anti-PD-1 agents (nivolumab, pembrolizumab, and cemiplimab) and three FDA-approved anti-PD-L1 agents (avelumab, durvalumab, and atezolizumab) approved for various cancer subtypes. PD-1 is the major inhibitory checkpoint expressed on T cells regulating their activation and helping to balance immune stimulation and protection against autoimmunity [10]. PD-

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L1 is expressed on a variety of cells, including other immune cells as well as cancer cells seeking to evade immune detection. Anti-PD(L)1 agents work by blocking the inhibitory signal transmitted by activation of the PD-1 receptor on T cells allowing for improved immune surveillance and cytotoxic killing of cancer cells that express viral or neoantigens that result from tumor genomic alterations [11, 12]. Many cancers for which these drugs are FDA-approved are more common in PLWH than in the general population. They are also attractive agents in PLWH as they do not cause further immunosuppression, unlike most traditional cytotoxic chemotherapies and radiotherapy.

However, these agents are not without toxicities. Under physiologic conditions, upregulation of these inhibitory receptors is important to dampen T cell receptor activation, prevent excessive cytokine production, and inhibit self-reactive T cells [13]. Given their mechanism of action, monoclonal antibodies targeting this pathway are associated with a series of well-characterized immune-related adverse events (irAE), including pneumonitis, colitis, hepatitis, dermatitis, and autoimmune endocrinopathies. Several professional organizations have published guidelines for managing irAE in people receiving immune checkpoint inhibitors [14, 15, 16•]. There is an additional concern that undiagnosed co-infections such as hepatitis B or hepatitis C virus may increase risk of irAE [17, 18]. Rare cases of *Mycobacterium (M) tuberculosis* immune reconstitution syndrome (TB-IRIS) have also been reported in people receiving immune checkpoint inhibitors [19]. In general, these irAEs respond to standard management, and do not preclude a favorable risk benefit ratio for some cancers.

PLWH have been excluded from all clinical trials of anti-PD1 and anti-PDL1 monoclonal antibodies leading to approval for cancer indications to date. To develop evidence for use in this patient population, several investigator-initiated studies have been completed or are underway to evaluate safety and activity in PLWH. Here, we summarize the known safety and efficacy data to justify the use of immunotherapy where indicated in PLWH and cancer and suggest monitoring and supportive care measures for PLWH and cancer receiving anti-PD-1 or anti-PD-L1 therapy. Future directions include evaluation in HIV-associated Kaposi sarcoma as well as in combination strategies in this underserved patient population.

HIV Effects on PD-1

There are several reasons PLWH may have decreased immunosurveillance and immune control of cancer. Profound $CD4^+$ T cell loss in those with advanced HIV leads to depletion of virus-specific T cells and allows for proliferation of virus-infected cells and development of cancer, such as in the cases of Epstein Barr virus (EBV), Kaposi sarcoma herpesvirus (KSHV), and human papilloma virus (HPV) causing B cell lymphomas, Kaposi sarcoma, and cervical cancer, respectively [20, 21]. However, even in the setting of well-controlled HIV with normal or near-normal $CD4^+$ counts, persistence of HIV and chronic viral antigenemia may lead to a loss of cytotoxic T cell function attributed to generalized $CD4^+$ and $CD8^+$ T cell upregulation of immune checkpoint proteins, including PD-1 [22]. In this state, T cells do not adequately proliferate or secrete cytokines leading to impaired ability to kill both virus-infected and cancer cells [23, 24].

In HIV, PD-1 expression correlates with viral load, $CD4^+$ count, and the cytotoxic function of $CD8^+$ cells [22, 25, 26]. PD-1 expression and exhaustion occur in both HIV-specific $CD4^+$ and $CD8^+$ T cells and potentially T cells specific for viral antigens or tumor neoantigens in PLWH [27, 28]. Exhaustion of $CD4^+$ T cells impairs their helping ability and impacts production of interleukin (IL)-2, INF-gamma, and TNF-alpha [27]. Additional inhibitory receptors may also be expressed on the cell surface, such as cytotoxic T lymphocyte antigen-4 (CTLA-4), lymphocyte activation gene protein (LAG-3), and T cell immunoglobulin domain and mucin domain-containing protein (TIM-3), T cell immunoreceptor with Ig and ITIM domains (TIGIT), CD160, and 2B4 (CD244) (Fig. 1) [10]. Treatment with ART reduces PD-1 expression and T cell exhaustion but not to existing levels prior to HIV infection [29].

Safety and Adverse Event Management of PD-1/PD-L1 Inhibitors in PLWH and Cancer

Recent prospective and retrospective data have demonstrated safety of PD-1 inhibitors in PLWH across many tumor types and $CD4^+$ T cell counts. There have been two recent publications of major prospective clinical trials focusing on safety in PLWH and advanced cancers. Cancer Immunotherapies Network Study-12 (CITN-12), a phase 1 multicenter study in the USA of 30 participants with controlled HIV and $CD4^+$ T cell counts greater than 100 cells/μL, demonstrated safety with the anti-PD-1 agent, pembrolizumab [30••]. Participants were enrolled in cohorts according to $CD4^+$ T cell counts (cohort 1: 100–200 $CD4^+$ T cells/μL, cohort 2: 200–350 $CD4^+$ T cells/μL, cohort 3: > 350 $CD4^+$ T cells/μL) with no difference in safety signals or irAEs between cohorts. More recently, results from the DURVAST phase 2 study of 20 participants demonstrated the safety of a PD-L1 agent, durvalumab, in PLWH and advanced cancer with $CD4^+$ T cell counts greater than 200 cells/μL that was conducted in European centers [31••]. Neither study showed an increase in serious irAEs in PLWH above that expected in the general population.

Studies have also shown there are no negative effects on $CD4^+$ T cell counts or HIV viral load. In addition to these two

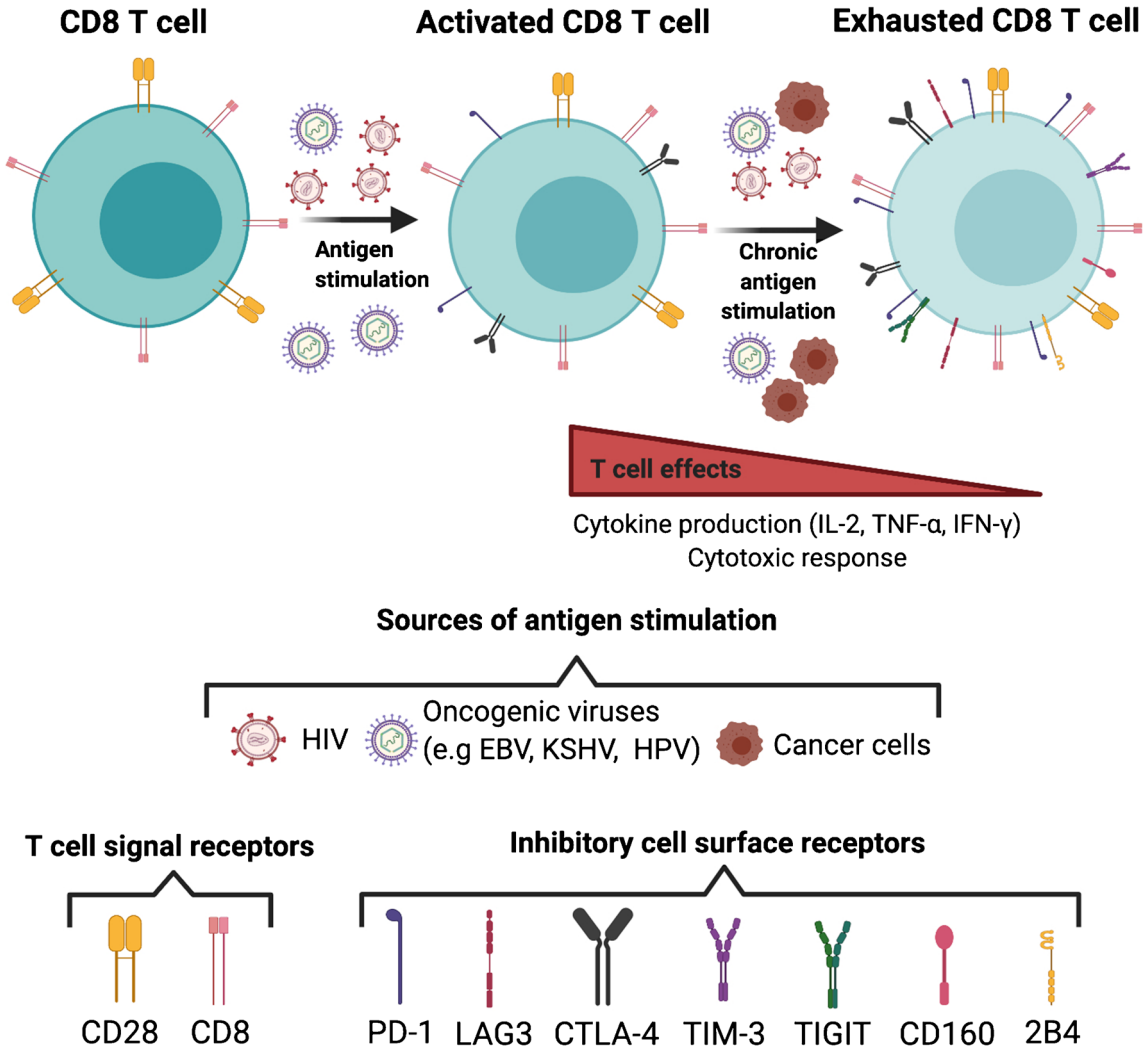

Fig. 1 T cell promoting and inhibiting surface antigens. Effector T cell activation upon recognition of antigen by a specific T cell receptor requires a CD8 co-receptor recognizing major histocompatibility complex-I and is regulated by stimulatory (CD28) and inhibitory immune checkpoints (PD-1, LAG3, CTLA-4, TIM-3, TIGIT, CD0160, 24B) that balance the function of immune surveillance with protection against autoimmunity and destruction of healthy tissues. Chronic T cell stimulation by HIV, oncogenic viruses, or cancer cells leads to increased immune checkpoint proteins with downstream changes in cell signaling leading to loss of cytotoxic response, or T cell "exhaustion". This figure was created on biorender.com

prospective trials, mounting retrospective evidence supports the safety of these agents across tumors that occur at higher rates among PLWH and incidental cancers [32•, 33, 34]. Similar to prospective studies, most retrospective case series have only included patients with higher $CD4^+$ T cell counts, and there is a paucity of evidence about safety in patients with severe $CD4^+$ lymphocytopenia with less than 100 cells/μL. This will be an important question to answer as cancer risk in PLWH is correlated with severity of $CD4^+$ lymphocytopenia for the AIDS-defining malignancies, KS, NHL, and cervical cancer and also for certain non-AIDS-defining malignancies, such as hepatocellular carcinoma, and head and neck cancers, for which there is FDA approval for treatment using multiple checkpoint inhibitors (Table 1) [35, 36]. If checkpoint inhibitors are used in PLWH, we recommend checking the $CD4^+$ T cell count and HIV viral load at baseline and then according to Infectious Diseases Society of America guidelines [37]. All patients should be treated with concurrent use of ART and in conjunction with an HIV specialist to ensure continued monitoring of HIV and any other chronic conditions.

There are established guidelines for the treatment of irAEs as recommended for the general population receiving checkpoint inhibitors, and unless evidence emerges to argue for special considerations, these should be utilized in PLWH who are receiving these therapies [16•]. This includes appropriate screening of participants before initiation of therapy and monitoring for adverse events [14, 15, 16•]. Autoimmune endocrinopathies are managed with hormone replacement, most commonly with levothyroxine

Table 1 Food and Drug Administration–approved indications for checkpoint inhibitors in AIDS-defining and non-AIDS-defining cancers strongly associated with HIV

Agent	Mechanism of action	Indication	Reason for approval
Atezolizumab	Anti-PD-L1	**Metastatic non-small cell lung cancer** (NSCLC)	
		•In combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations	•Atezolizumab + bevacizumab/paclitaxel/carboplatin improved median OS from 14.7 months to 19.2 months compared with bevacizumab/paclitaxel/carboplatin [81]
		•In combination with nab-paclitaxel and carboplatin for the first-line treatment of metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations	•Atezolizumab + nab-paclitaxel/carboplatin improved median OS from 13.9 months to 18.6 months when compared with paclitaxel protein-bound/carboplatin [82]
		•As a single agent in metastatic NSCLC with progression during or following platinum-containing chemotherapy	•Atezolizumab improved median OS from 9.6 months to 13.8 months when compared with docetaxel [83]
Avelumab	Anti-PD-L1	**Metastatic Merkel cell carcinoma**	•ORR 33%; DOR 2.8 to 23.3+ months; DOR ≥ 6 months 86% [84]
Durvalumab	Anti-PD-L1	**Unresectable, stage III non-small cell lung cancer** without disease progression following concurrent platinum-based chemotherapy and radiation therapy	•Median OS not reached and PFS 16.8 months in patients receiving durvalumab compared with median OS 28.7 months and PFS 5.6 months in placebo arm [85]
Nivolumab	Anti-PD-1	**Metastatic non-small cell lung cancer** with progression on or after platinum-based chemotherapy	•Median OS 9.2 months, PFS 3.5 months, ORR 20% with nivolumab compared with median OS 6.0 months, PFS 2.8 months, ORR 9% with docetaxel [86]
		Classical Hodgkin lymphoma that has relapsed or progressed after •Autologous HSCT and brentuximab vedotin, or •3 or more lines of systemic therapy that includes autologous HSCT	•Combined ORR 66%, median DOR 13.1 months in two prospective studies that included patients with classical Hodgkin lymphoma after HSCT and brentuximab vedotin [7, 87]
		Recurrent or metastatic **squamous cell carcinoma of the head and neck** with disease progression on or after a platinum-based therapy	•Median OS 7.5 months, PFS at 6 months 19.7% with nivolumab compared with 5.1 months PFS 9.9% with investigator's choice of treatment [88]
		Hepatocellular carcinoma previously treated with sorafenib, as a single agent or in combination with ipilimumab	•ORR 14%, DOR 4.6 to 30.5+ months with nivolumab and ORR 33%, DOR 3.2–51.1+ months with nivolumab + ipilimumab [46••, 89]
Pembrolizumab	Anti-PD-1	**Non-small cell lung cancer** (NSCLC)	•Median OS not reached; PFS 8.8 months with pembrolizumab + pemetrexed/platinum chemotherapy compared with median OS 11.3 months; PFS 4.9 months with pemetrexed/platinum chemotherapy alone [90]
		•In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations	•Pembrolizumab + carboplatin/(nab-)paclitaxel improved median OS from 11.3 months to 15.9 months compared with carboplatin/(nab-)paclitaxel alone [91]
		•In combination with carboplatin and either paclitaxel or nab-paclitaxel, as first-line treatment of patients with metastatic squamous NSCLC	•Pembrolizumab improved median OS from 14.2 months with standard chemotherapy to 30 months [92] in previously untreated patients with metastatic disease
		•As a single agent for NSCLC that expresses ≥ 1% PD-L1 and is metastatic or stage III and unresectable or not a candidate for definitive radiation	
		•As a single agent for metastatic NSCLC that expresses ≥ 1% PD-L1 with disease progression on or after platinum-containing chemotherapy	
		Merkel cell carcinoma	•ORR 56%, CR rate 24%, DOR 5.9–34.5+ months, DOR ≥ 6 months 96%, DOR ≥ 12 months 54% [93]
		Head and neck squamous cell cancer (HNSCC)	•Median OS 13 months with pembrolizumab + platinum/fluorouracil compared with 10.7 months with cetuximab + platinum/fluorouracil [94]
		•In combination with platinum and fluorouracil for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC	•Median OS 12.3 months with pembrolizumab alone compared with 10.3 months with cetuximab/platinum/fluorouracil [94]
		•As a single agent for the first-line treatment metastatic or unresectable, recurrent HNSCC that expresses PD-L1	•ORR 18% with median DOR not reached (range: 2.4–30 months) and 85% of responses lasting ≥ 6 months with pembrolizumab in recurrent or progressive HNSCC after platinum-containing chemotherapy [95]
		•As a single agent for recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy	
		Classical Hodgkin lymphoma that is refractory or relapsed after 3 or more prior lines of therapy	•ORR 69%, CR rate 22% and median DOR 11.1 months [96]
		Cervical cancer that is recurrent or metastatic with disease progression on or after chemotherapy whose tumors express PD-L1	•ORR 14.3% with median DOR not reached and 91% with DOR ≥ 6 months [72]
		Hepatocellular carcinoma previously treated with sorafenib	•ORR 17% with DOR ≥ 6 months 89% and DOR ≥ 12 months 56% [47••]

ALK indicates anaplastic lymphoma kinase; *DOR*, duration of response; *EGFR*, epide4rmal growth factor receptor; *HSCT*, hematopoietic stem cell transplant; *ORR*, overall response rate; *OS*, overall survival; *PFS*, progression-free survival

for hypothyroidism. Serious irAEs generally are treated with high-dose corticosteroids, with additional agents such as monoclonal antibodies targeting tumor necrosis factor-alpha (TNF-a) or mycophenolate reserved for use in refractory cases.

Studies of Immune Checkpoint Inhibitors in Kaposi Sarcoma

Given its close association with immunosuppression in PLWH, checkpoint inhibitor therapy is a promising class of agents in KS. There are two ongoing studies evaluating anti-PD-1 therapy specifically in KS. CITN-12 is evaluating standard 200 mg IV pembrolizumab every 3 weeks for HIV-associated KS that has not responded to at least 3 months of ART, both in the first line and refractory settings [38]. A separate study of low-dose intralesional nivolumab in HIV-associated and HIV-negative KS is being evaluated at University of California, San Francisco [39]. Retrospective experience with anti-PD-1 therapy in nine patients with HIV-associated KS demonstrated a partial response or better in 67% of patients as well as 63% of eight patients included in a meta-analysis supporting research of anti-PD-(L)1 therapy as a potentially useful approach [32, 40].

There may be additional safety considerations when using anti-PD-(L)1 therapy in people with HIV-associated KS. In CITN-12, one patient with KS on the prospective study using pembrolizumab who had an elevated Kaposi sarcoma herpesvirus (KSHV, also known as human herpesvirus 8) viral load prior to treatment developed a progressive polyclonal KSHV-associated B cell lymphoproliferation and died [30••]. The elevated KSHV viral load prior to pembrolizumab treatment raises the concern that the participant may have had concurrent KSHV-associated multicentric Castleman disease (KSHV-MCD) or KSHV inflammatory cytokine syndrome (KICS), which are interleukin-6-related disorders associated with fevers, night sweats, weight loss, edema, hepatosplenomegaly, cytopenias, elevated inflammatory markers, and elevated KSHV viral load [41, 42]. While post-mortem evaluations in this patient were inconclusive as to the presence of either of these processes, investigators felt the KSHV lymphoproliferation was possibly attributed to pembrolizumab. This has not been observed in seven other participants in the published CITN-12 study with KSHV-associated malignancies or any participants with KS in an ongoing expansion cohort. While the incidence of concurrent KSHV-MCD among patients with KS is unknown, it is certainly underreported, and physicians need to exercise caution when treating KS with checkpoint inhibitors who have symptoms consistent with KSHV-MCD or KICS until more is known about whether these patients may develop exacerbation of these KSHV-related diseases [43]. For the ongoing prospective KS cohort in CITN-12, we have attempted to mitigate this risk by excluding patients with known active KSHV-MCD or active KICS as well as anemia (hemoglobin < 10 g/dL) or thrombocytopenia (platelets < lower limit of normal) that may be suggestive of these diseases. More specifically, prospective measurement of the KSHV/HHV8 viral load in patients with KS receiving checkpoint inhibitors may help identify patients at risk for KSHV-MCD, KICS, or other KSHV-associated lymphoproliferations that may possibly worsen with checkpoint inhibitor therapy. KSHV-MCD is generally responsive to rituximab, and while corticosteroids are sometimes administered during acute flares, more definitive treatment is essential [44, 45]. With these safety considerations, development of anti-PD-1-targeted therapy for the treatment of KS is warranted as there is an unmet clinical need for effective immunotherapy for HIV-associated KS.

Safety of Anti-PD-1/PD-L1 Monoclonal Antibodies in PLWH and Co-infections

Co-infections are important to consider in PLWH prior to administration of checkpoint inhibitors, particularly chronic viral infections, such as hepatitis B virus (HBV) and hepatitis C virus (HCV). This is particularly important as pembrolizumab and nivolumab are now both approved for the second-line treatment of hepatocellular carcinoma, which is often caused by HBV and HCV in PLWH. Similar to PLWH, patients with HBV and HCV were left out of the early trials with checkpoint inhibitors. In the trials that led to FDA approval of pembrolizumab and nivolumab in patients previously treated with sorafenib, patients with both HCV and HBV were enrolled [46••, 47••]. Participants with HBV received antiviral prophylaxis, and none had reactivation of HBV during treatment. Participants could have either treated or untreated HCV and no significant increases in HCV viral loads were seen in either trial.

A large retrospective trial of 114 patients with known HBV prior to checkpoint inhibitor therapy showed reactivation occurred in a small percentage of patients positive for HBV surface antigen and an undetectable HBV viral load who were not receiving prophylactic antiviral therapy [48•]. These patients received HBV treatment, and all had undetectable HBV DNA within a matter of weeks. No patient with detectable HBV receiving antiviral prophylaxis developed HBV reactivation during checkpoint inhibitor therapy. Importantly, reactivation did not appear to increase the risk of immune hepatitis and HBV reactivation appears preventable with appropriate prophylaxis. PLWH and concurrent HBV should receive an ART regimen with activity against both HIV and HBV that contains tenofovir disoproxil fumarate or tenofovir alafenamide in addition to either lamivudine or emtricitabine irrespective of checkpoint inhibitor therapy [49]. There is less known about the safety of checkpoint inhibitors in patients with HCV, but there have been case reports and small case series in addition to the previously mentioned prospective trials reporting safety without HCV flare or increased incidence of immune hepatitis in patients with HCV [50, 51].

There are no significant interactions between antiviral agents to treat HCV and anti-PD-1 therapies. We recommend that PLWH and cancer be evaluated for HBV and HCV before initiating anti-PD-1 or PD-L1 therapy, and if positive, be evaluated for appropriate concurrent antiviral therapy as well as monitoring of liver function and HBV and HCV viral control.

Infection with *M. tuberculosis* is also an important coinfection to consider prior to initiating treatment with checkpoint inhibitors. The risk of infection in PLWH is more than 50 times higher than in the general population worldwide [52]. *M. tuberculosis* may also increase the risk for lung cancer as well as other types of cancer, further increasing the chance that oncologists and HIV specialists will be treating patients with HIV, cancer, and tuberculosis [53, 54]. Monoclonal antibodies targeting the PD-1 pathway increase $CD4^+$ T cell activity and T helper type 1 immune responses. Mouse models show enhanced $CD4^+$ T cell activity exacerbates *M. tuberculosis* and PD-1 knockout mice experience more severe *M. tuberculosis* infections [55–57]. In addition, exposure to *M. tuberculosis* activates natural killer cells, which increases PD-1 and PD-L1 expression on these cells serving as a protective mechanism against excess tissue damage [58]. Both acute infection and TB-IRIS have been described in patients receiving checkpoint inhibitors, including patients where there was no suspicion of active *M. tuberculosis* prior to a tuberculin skin test or interferon gamma release assay (IGRA) [59•, 60]. There are no guidelines recommending *M. tuberculosis* testing prior to anti-PD-(L)1 therapy. In alignment with guidelines for PLWH from the Department of Health and Human Services for PLWH, we advocate documenting tuberculosis testing and treatment history for all PLWH with unknown TB status prior to receiving these therapies given the significant increased risk of *M. tuberculosis* infection in this population. Patients with a positive IGRA should be evaluated for signs of active *M. tuberculosis* with chest imaging and treated according to published guidelines with careful consideration of potential drug-drug interactions [61]. It is imperative to know patients' status and to treat latent cases to prevent TB-IRIS. TNF-alpha inhibitors, particularly infliximab, are associated with reactivation of latent *M. tuberculosis* and severe infections [62].

Efficacy of PD-1/PD-L1 Inhibitors in PLWH and Cancer

The two reported prospective trials of PLWH and advanced cancer enrolled heterogeneous groups of tumor types and $CD4^+$ T cell counts, however, tumor responses were noted in patients with NSCLC, non-Hodgkin lymphoma, and KS [30••, 31••]. The evidence for efficacy in NSCLC is particularly strong and has been reported across $CD4^+$ T cell counts, including in those < 100 cells/μL [34, 63, 64]. There may be a reason to expect a clinically meaningful tumor response rate in PLWH and NSCLC as one study showed tumors from PLWH and HIV-negative controls showed significantly higher PD-L1 expression in tumor cells and tumor-infiltrating lymphocytes in the tumors from PLWH, which tend to correlate with response to anti-PD-(L)1 therapies [65]. A major reason for the exclusion of PLWH from prospective trials of checkpoint inhibitors has been a concern for decreased efficacy. While more data are needed, it is our experience that patients with $CD4^+$ T cell counts less than 100 cells/μL can have tumor responses to these agents and this treatment should not be excluded in such patients when approved for their tumor.

As retrospective and prospective studies have demonstrated safety of anti-PD-(L)1 agents, strong consideration should be given to utilize anti-PD-(L)1 agents in PLWH where indicated [66••]. There are currently FDA-approved indications for anti-PD-(L)1 therapy in classical Hodgkin lymphoma, non-small cell lung cancer (NSCLC), cervical cancer, squamous cell cancer of the head and neck cancer, Merkel cell carcinoma, and hepatocellular carcinoma (Table 1). Although not FDA-approved, nivolumab and pembrolizumab are incorporated into treatment guidelines for metastatic anal squamous cell carcinoma based upon early phase trials due to the lack of treatment options in this disease [67]. In a phase 2 trial of refractory metastatic anal cancer treated with nivolumab, there was an ORR of 24%, PFS of 4.1 months, and median OS of 11.5 months. PLWH were eligible to enroll in this study if their CD4+ T cell count was > 300 cell/μL and HIV viral was undetectable. Two HIV-positive participants were enrolled with one having a partial response [68]. A phase 1b study of pembrolizumab that excluded PLWH showed an ORR of 17% in metastatic recurrent anal cancer has also been reported [69].

Future Directions

In spite of progress in the field of immuno-oncology, there is still significant need for improvement in the therapy of cancers affecting PLWH. While promising durable responses have been observed in a significant minority of patients with certain malignancies receiving anti-PD-(L)1 agents, the majority of patients do not have decreases in tumor volume. In addition to determining predictors of response to treatment, oncologists are evaluating strategies to incorporate anti-PD-(L)1 therapy earlier in the course of disease, as well as to improve response rates in those with advanced cancer by combining checkpoint inhibitors or blocking mechanisms of resistance in the tumor microenvironment. Combination immunotherapy is particularly attractive in PLWH as they have increased upregulation of immune checkpoints due to T cell exhaustion compared with the general population. Combination immunotherapy for PLWH and advanced cancers is already underway through the AIDS Malignancy Consortium combining nivolumab and ipilimumab, a CTLA-4 inhibitor [70]. Single-agent and

combination trials are underway in the general population with agents targeting LAG3, TIM3, and TIGIT.

Immune checkpoint inhibitors are theoretically attractive for use in AIDS-defining malignancies where avoiding immunosuppressive chemotherapy is desirable. In addition, virus-driven tumors, such as KS, cervical cancer, and certain NHLs, may have increased T cell exhaustion due to further chronic viral stimulation adding to the rationale for the use of checkpoint inhibitors for these tumors. Unlike classical Hodgkin lymphoma, anti-PD(L)1 agents have not shown significant activity in the majority of NHL in the general population. In diffuse large B cell lymphoma, the most common subtype of NHL in PLWH, response rates to anti-PD-(L)1 agents is less than 10% [71]. It is unknown, however, if PLWH who have higher proportions of exhausted T cells and upregulation of PD-1 on their T cells may have higher response rates to checkpoint inhibitors. CITN-12 enrolled five participants with NHL, two with partial response and two with prolonged stable disease suggesting improved outcomes in PLWH and NHL [30••]. Also, given the intermittent long-term chemotherapy required to treat KS in certain patients, checkpoint inhibitors hold special promise to improve outcomes. Pembrolizumab is being investigated in the frontline setting as a way to avoid further immunosuppression from chemotherapy in already immunocompromised patients [38]. Pembrolizumab is approved for treatment of progressive metastatic cervical cancer after treatment with standard chemotherapy based upon durable responses lasting over 6 months in more than 90% of responding tumors, although the overall response rate was only around 14% in the phase 2 study that led to approval [72]. Combination approaches that further target inhibitory signals in the tumor microenvironment or increase antigen presentation may increase response rates in HIV-associated cancers [73]. For example, transforming growth factor-beta (TGF-beta) has been found to be a source of checkpoint inhibitor resistance and is significantly overly expressed in cervical cancer and other HPV-related cancers. Targeting of both PD-L1 and TGF-beta has shown to increase response rates and duration of response in HPV-driven cancers [74, 75]. There is currently an ongoing trial evaluating this approach specially in HPV-associated tumors [76]. Targeting TGF-beta and the PD-1 pathway is also being combined with tumor-directed interleukin-12 to induce cytotoxic T and NK cell function to treat patients with relapsed KS in a clinical trial [77]. The number of trials of combination immunotherapy across tumor types is expanding rapidly and we hope PLWH will be included in these trials per guidance by the American Society of Clinical Oncology [78].

Conclusions

Anti-PD-(L)1 agents have significant promise to treat a wide variety of cancers in PLWH. More investigation must be done to optimize their use in the first-line setting and improve response rates to these agents and overall survival for the growing number of people developing cancer as the population of PLWH ages thanks to advances in ART. Literature on health disparities in the cancer care of PLWH suggest that oncologists are reticent to offer new therapies for cancer but advocacy efforts are underway to change this mentality [79, 80]. It is important that HIV and infectious disease experts work closely with oncologists to facilitate safe treatment options for PLWH and cancer, taking into consideration the risks and benefits of agents such as immunotherapies. Where feasible, a multidisciplinary approach needs to be adopted in the diagnosis and management of PLWH and cancer.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Sabin CA. Do people with HIV infection have a normal life expectancy in the era of combination antiretroviral therapy? BMC Med. 2013;11:251.
2. • Yarchoan R, Uldrick TS. HIV-associated cancers and related diseases. N Engl J Med. 2018;378(11):1029–41 **This is a review of HIV-associated cancers for general reference.**
3. Pantanowitz L, Dezube BJ. Evolving spectrum and incidence of non-AIDS-defining malignancies. Curr Opin HIV AIDS. 2009;4(1):27–34.
4. Gopal S, Patel MR, Yanik EL, Cole SR, Achenbach CJ, Napravnik S, et al. Temporal trends in presentation and survival for HIV-associated lymphoma in the antiretroviral therapy era. J Natl Cancer Inst. 2013;105(16):1221–9.
5. Robbins HA, Pfeiffer RM, Shiels MS, Li J, Hall HI, Engels EA. Excess cancers among HIV-infected people in the United States. Natl Cancer Inst. 2015;107(4):dju503.
6. Shiels MS, Islam JY, Rosenberg PS, Hall HI, Jacobson E, Engels EA. Projected cancer incidence rates and burden of incident cancer cases in HIV-infected adults in the United States through 2030. Ann Intern Med. 2018;168(12):866–73.
7. Armand P, Engert A, Younes A, Fanale M, Santoro A, Zinzani PL, Timmerman JM, Collins GP, Ramchandren R, Cohen JB, de Boer JP, Kuruvilla J, Savage KJ, Trneny M, Shipp MA, Kato K, Sumbul A, Farsaci B, Ansell SM Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm phase II CheckMate 205 trial. J Clin Oncol 2018;36(14):1428–1439.
8. Gandhi L, Garassino MC. Pembrolizumab plus chemotherapy in lung cancer. N Engl J Med. 2018;379(11):e18.
9. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2019;381(16):1535–46.
10. Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. Nat Rev Immunol. 2015;15(8):486–99.
11. Stevanovic S, Pasetto A, Helman SR, Gartner JJ, Prickett TD, Howie B, et al. Landscape of immunogenic tumor antigens in

successful immunotherapy of virally induced epithelial cancer. Science. 2017;356(6334):200–5.
12. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. N Engl J Med. 2017;377(25):2500–1.
13. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev. 2010;236:219–42.
14. Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, Budde LE, Costa L, Davies M, Dunnington D, Ernstoff MS, Frigault M, Kaffenberger BH, Lunning M, McGettigan S, McPherson J, Mohindra NA, Naidoo J, Olszanski AJ, Oluwole O, Patel SP, Pennell N, Reddy S, Ryder M, Santomasso B, Shofer S, Sosman JA, Wang Y, Weight RM, Johnson-Chilla A, Zuccarino-Catania G, Engh A NCCN guidelines insights: management of immunotherapy-related toxicities, version 1.2020. J Natl Compr Cancer Netw 2020;18(3):230–241.
15. Puzanov I, Diab A, Abdallah K, Bingham CO 3rd, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5(1):95.
16.• Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714–68 **These are the American Society of Clinic Oncology guidelines for the management of immune-related adverse events caused by immune checkpoint inhibitors.**
17. Byeon S, Cho JH, Jung HA, Sun JM, Lee SH, Ahn JS, et al. PD-1 inhibitors for non-small cell lung cancer patients with special issues: real-world evidence. Cancer Med. 2020;9(7):2352–62.
18. Gardiner D, Lalezari J, Lawitz E, DiMicco M, Ghalib R, Reddy KR, et al. A randomized, double-blind, placebo-controlled assessment of BMS-936558, a fully human monoclonal antibody to programmed death-1 (PD-1), in patients with chronic hepatitis C virus infection. PLoS One. 2013;8(5):e63818.
19. Barber DL, Sakai S, Kudchadkar RR, Fling SP, Day TA, Vergara JA, et al. Tuberculosis following PD-1 blockade for cancer immunotherapy. Sci Transl Med. 2019;11(475).
20. Martinez-Maza O, Breen EC. B-cell activation and lymphoma in patients with HIV. Curr Opin Oncol. 2002;14(5):528–32.
21. de Martel C, Shiels MS, Franceschi S, Simard EP, Vignat J, Hall HI, et al. Cancers attributable to infections among adults with HIV in the United States. AIDS. 2015;29(16):2173–81.
22. Trautmann L, Janbazian L, Chomont N, Said EA, Gimmig S, Bessette B, et al. Upregulation of PD-1 expression on HIV-specific CD8+ T cells leads to reversible immune dysfunction. Nat Med. 2006;12(10):1198–202.
23. Zajac AJ, Blattman JN, Murali-Krishna K, Sourdive DJ, Suresh M, Altman JD, et al. Viral immune evasion due to persistence of activated T cells without effector function. J Exp Med. 1998;188(12):2205–13.
24. Yi JS, Cox MA, Zajac AJ. T-cell exhaustion: characteristics, causes and conversion. Immunology. 2010;129(4):474–81.
25. Day CL, Kaufmann DE, Kiepiela P, Brown JA, Moodley ES, Reddy S, et al. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. Nature. 2006;443(7109):350–4.
26. Blackburn SD, Shin H, Haining WN, Zou T, Workman CJ, Polley A, et al. Coregulation of CD8+ T cell exhaustion by multiple inhibitory receptors during chronic viral infection. Nat Immunol. 2009;10(1):29–37.
27. D'Souza M, Fontenot AP, Mack DG, Lozupone C, Dillon S, Meditz A, et al. Programmed death 1 expression on HIV-specific CD4+ T cells is driven by viral replication and associated with T cell dysfunction. J Immunol. 2007;179(3):1979–87.
28. Kaufmann DE, Kavanagh DG, Pereyra F, Zaunders JJ, Mackey EW, Miura T, et al. Upregulation of CTLA-4 by HIV-specific CD4+ T cells correlates with disease progression and defines a reversible immune dysfunction. Nat Immunol. 2007;8(11):1246–54.
29. Fenwick C, Joo V, Jacquier P, Noto A, Banga R, Perreau M, et al. T-cell exhaustion in HIV infection. Immunol Rev. 2019;292(1):149–63.
30.•• Uldrick TS, Goncalves PH, Abdul-Hay M, Claeys AJ, Emu B, Ernstoff MS, et al. Assessment of the safety of pembrolizumab in patients with HIV and advanced cancer-a phase 1 study. JAMA Oncol. 2019;5(9):1332–9 **These are the published results of CITN-12, the first prospective study of pembrolizumab in people living with HIV and advanced cancers.**
31.•• Gonzalez-Cao M, Moran T, Dalmau J, Garcia-Corbacho J, Bracht JWP, Bernabe R, et al. Assessment of the feasibility and safety of durvalumab for treatment of solid tumors in patients with HIV-1 infection: the phase 2 DURVAST study. JAMA Oncol. 2020; **These are the published results of the DURVAST study, a phase II study of durvalumab in people living with HIV and advanced cancers.**
32.• Cook MR, Kim C. Safety and efficacy of immune checkpoint inhibitor therapy in patients with HIV infection and advanced-stage cancer: a systematic review. JAMA Oncol. 2019; **This is a systematic review reporting the safety of anti-PD-1 and anti-PD-L1 therapies in people living with HIV and cancer.**
33. Spano JP, Veyri M, Gobert A, Guihot A, Perre P, Kerjouan M, et al. Immunotherapy for cancer in people living with HIV: safety with an efficacy signal from the series in real life experience. AIDS. 2019;33(11):F13–F9.
34. Chang E, Sabichi AL, Kramer JR, Hartman C, Royse KE, White DL, et al. Nivolumab treatment for cancers in the HIV-infected population. J Immunother. 2018;41(8):379–83.
35. Hernández-Ramírez RU, Shiels MS, Dubrow R, Engels EA. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. Lancet HIV. 2017;4(11):e495–504.
36. Clifford GM, Franceschi S. Cancer risk in HIV-infected persons: influence of CD4+ count. Future Oncol. 2009;5(5):669–78.
37. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA, et al. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2014;58(1):1–10.
38. NCT02595866. Pembrolizumab in treating patients with HIV and relapsed, refractory, or disseminated malignant neoplasms. https://clinicaltrials.gov/ct2/show/NCT02595866. Accessed April 1, 2020.
39. NCT03316274. Intra-lesional nivolumab therapy for limited cutaneous Kaposi sarcoma. https://clinicaltrials.gov/ct2/show/NCT03316274. Accessed April 1, 2020.
40. Galanina N, Goodman AM, Cohen PR, Frampton GM, Kurzrock R. Successful treatment of HIV-associated Kaposi sarcoma with immune checkpoint blockade. Cancer Immunol Res. 2018;6(10):1129–35.
41. Lurain K, Yarchoan R, Uldrick TS. Treatment of Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. Hematol Oncol Clin North Am. 2018;32(1):75–88.
42. Polizzotto MN, Uldrick TS, Wyvill KM, Aleman K, Marshall V, Wang V, et al. Clinical features and outcomes of patients with symptomatic Kaposi sarcoma herpesvirus (KSHV)-associated inflammation: prospective characterization of KSHV inflammatory cytokine syndrome (KICS). Clin Infect Dis. 2016;62(6):730–8.
43. Ramaswami R, Lurain K, Goncalves PH, Polizzotto M, Widell A, Lindsley M, Little RF, Uldrick TS, Yarchoan R. Long-term outcomes of 58 patients with HIV and KSHV+ multicentric Castleman

disease [CROI Abstract 17]. In Special issue: Abstracts from the 2019 Conference on Retroviruses and Opportunistic Infections Top Antivir Med 2019;27(suppl 1):5.

44. Gerard L, Berezne A, Galicier L, Meignin V, Obadia M, De Castro N, et al. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus associated multicentric Castleman's disease: ANRS 117 CastlemaB Trial. J Clin Oncol. 2007;25(22):3350–6.
45. Bower M, Powles T, Williams S, Davis TN, Atkins M, Montoto S, et al. Brief communication: rituximab in HIV-associated multicentric Castleman disease. Ann Intern Med. 2007;147(12):836–9.
46.•• El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017;389(10088):2492–502 **These are the published results of CheckMate 040 demonstrating efficacy and safety of nivolumab in advanced hepatocellular carcinoma that included participants with hepatitis B and C.**
47.•• Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018;19(7):940–52 **These are the published results of KEYNOTE-224 demonstrating efficacy and safety of pembrolizumab in advanced hepatocellular carcinoma that included participants with hepatitis B and C.**
48.• Zhang X, Zhou Y, Chen C, Fang W, Cai X, Zhang X, et al. Hepatitis B virus reactivation in cancer patients with positive Hepatitis B surface antigen undergoing PD-1 inhibition. J Immunother Cancer. 2019;7(1):322 **This is a retrospecitve case series of 114 patients with hepatitis B infection treated with anti-PD-(L)1 therapies demonstrating no increased risk of immune-related hepatitis and efficacy of antiviral prophylaxis to prevent hepatitis B reactivation.**
49. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed April 20, 2020.
50. Shah NJ, Al-Shbool G, Blackburn M, Cook M, Belouali A, Liu SV, et al. Safety and efficacy of immune checkpoint inhibitors (ICIs) in cancer patients with HIV, hepatitis B, or hepatitis C viral infection. J Immunother Cancer. 2019;7(1):353.
51. Kothapalli A, Khattak MA. Safety and efficacy of anti-PD-1 therapy for metastatic melanoma and non-small-cell lung cancer in patients with viral hepatitis: a case series. Melanoma Res. 2018;28(2):155–8.
52. Getahun H, Gunneberg C, Granich R, Nunn P. HIV infection-associated tuberculosis: the epidemiology and the response. Clin Infect Dis. 2010;50(Suppl 3):S201–7.
53. Yu YH, Liao CC, Hsu WH, Chen HJ, Liao WC, Muo CH, et al. Increased lung cancer risk among patients with pulmonary tuberculosis: a population cohort study. J Thorac Oncol. 2011;6(1):32–7.
54. Vento S, Lanzafame M. Tuberculosis and cancer: a complex and dangerous liaison. Lancet Oncol. 2011;12(6):520–2.
55. Tousif S, Singh Y, Prasad DV, Sharma P, Van Kaer L, Das G. T cells from Programmed Death-1 deficient mice respond poorly to Mycobacterium tuberculosis infection. PLoS One. 2011;6(5):e19864.
56. Lazar-Molnar E, Chen B, Sweeney KA, Wang EJ, Liu W, Lin J, et al. Programmed death-1 (PD-1)-deficient mice are extraordinarily sensitive to tuberculosis. Proc Natl Acad Sci U S A. 2010;107(30):13402–7.
57. Barber DL, Mayer-Barber KD, Feng CG, Sharpe AH, Sher A. CD4 T cells promote rather than control tuberculosis in the absence of PD-1-mediated inhibition. J Immunol. 2011;186(3):1598–607.
58. Alvarez IB, Pasquinelli V, Jurado JO, Abbate E, Musella RM, de la Barrera SS, et al. Role played by the programmed death-1-programmed death ligand pathway during innate immunity against Mycobacterium tuberculosis. J Infect Dis. 2010;202(4):524–32.
59.• Langan EA, Graetz V, Allerheiligen J, Zillikens D, Rupp J, Terheyden P. Immune checkpoint inhibitors and tuberculosis: an old disease in a new context. Lancet Oncol. 2020;21(1):e55–65 **This is a case series and review of tuberculosis reactivation in patients with cancer treated with immune checkpoint inhibitors.**
60. Anastasopoulou A, Ziogas DC, Samarkos M, Kirkwood JM, Gogas H. Reactivation of tuberculosis in cancer patients following administration of immune checkpoint inhibitors: current evidence and clinical practice recommendations. J Immunother Cancer. 2019;7(1):239.
61. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016;63(7):e147–e95.
62. Murdaca G, Negrini S, Pellecchio M, Greco M, Schiavi C, Giusti F, et al. Update upon the infection risk in patients receiving TNF alpha inhibitors. Expert Opin Drug Saf. 2019;18(3):219–29.
63. Ostios-Garcia L, Faig J, Leonardi GC, Adeni AE, Subegdjo SJ, Lydon CA, et al. Safety and efficacy of PD-1 inhibitors among HIV-positive patients with non-small cell lung cancer. J Thorac Oncol. 2018;13(7):1037–42.
64. Hentrich M, Schipek-Voigt K, Jager H, Schulz S, Schmid P, Stotzer O, et al. Nivolumab in HIV-related non-small-cell lung cancer. Ann Oncol. 2017;28(11):2890.
65. Domblides C, Antoine M, Hamard C, Rabbe N, Rodenas A, Vieira T, et al. Nonsmall cell lung cancer from HIV-infected patients expressed programmed cell death-ligand 1 with marked inflammatory infiltrates. AIDS. 2018;32(4):461–8.
66.•• Reid E, Suneja G, Ambinder RF, Ard K, Baiocchi R, Barta SK, et al. Cancer in people living with HIV, version 1.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2018;16(8):986–1017 **These are the National Comprehensive Cancer Network guidelines for the treatment of cancer in people living with HIV.**
67. Benson AB, Venook AP, Al-Hawary MM, Cederquist L, Chen YJ, Ciombor KK, et al. NCCN guidelines insights: colon cancer, version 2.2018. J Natl Compr Cancer Netw. 2018;16(4):359–69.
68. Morris VK, Salem ME, Nimeiri H, Iqbal S, Singh P, Ciombor K, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2017;18(4):446–53.
69. Ott PA, Piha-Paul SA, Munster P, Pishvaian MJ, van Brummelen EMJ, Cohen RB, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal. Ann Oncol. 2017;28(5):1036–41.
70. NCT02408861. Nivolumab and ipilimumab in treating patients with HIV associated relapsed or refractory classical Hodgkin lymphoma or solid tumors that are metastatic or cannot be removed by surgery. https://clinicaltrials.gov/ct2/show/NCT02408861. Accessed April 1, 2020.
71. Ansell SM, Minnema MC, Johnson P, Timmerman JM, Armand P, Shipp MA, et al. Nivolumab for relapsed/refractory diffuse large B-cell lymphoma in patients ineligible for or having failed autologous transplantation: a single-arm, phase II study. J Clin Oncol. 2019;37(6):481–9.
72. Chung HC, Ros W, Delord JP, Perets R, Italiano A, Shapira-Frommer R, et al. Efficacy and safety of pembrolizumab in

previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol. 2019;37(17):1470–8.
73. Davis DA, Shrestha P, Aisabor AI, Stream A, Galli V, Pise-Masison CA, et al. Pomalidomide increases immune surface marker expression and immune recognition of oncovirus-infected cells. Oncoimmunology. 2019;8(2):e1546544.
74. Strauss J, Heery CR, Schlom J, Madan RA, Cao L, Kang Z, et al. Phase I trial of M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGFbeta, in advanced solid tumors. Clin Cancer Res. 2018;24(6):1287–95.
75. Lind H, Gameiro SR, Jochems C, Donahue RN, Strauss J, Gulley JM, et al. Dual targeting of TGF-beta and PD-L1 via a bifunctional anti-PD-L1/TGF-betaRII agent: status of preclinical and clinical advances. J Immunother Cancer. 2020;8(1):e000433.
76. NCT03427411. M7824 in subjects with HPV associated malignancies. https://clinicaltrials.gov/ct2/show/NCT03427411. Accessed April 1, 2020.
77. NCT04303117. NHS-IL12 monotherapy and in combination with M7824 in advanced Kaposi sarcoma. https://clinicaltrials.gov/ct2/show/NCT04303117. Accessed April 1, 2020.
78. Uldrick TS, Ison G, Rudek MA, Noy A, Schwartz K, Bruinooge S, et al. Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology-friends of Cancer Research HIV Working Group. J Clin Oncol. 2017;35(33):3774–80.
79. Suneja G, Shiels MS, Melville SK, Williams MA, Rengan R, Engels EA. Disparities in the treatment and outcomes of lung cancer among HIV-infected individuals. AIDS. 2013;27(3):459–68.
80. Suneja G, Shiels MS, Angulo R, Copeland GE, Gonsalves L, Hakenewerth AM, et al. Cancer treatment disparities in HIV-infected individuals in the United States. J Clin Oncol. 2014;32(22):2344–50.
81. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378(24):2288–301.
82. West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(7):924–37.
83. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255–65.
84. Kaufman HL, Russell JS, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Updated efficacy of avelumab in patients with previously treated metastatic Merkel cell carcinoma after >/=1 year of follow-up: JAVELIN Merkel 200, a phase 2 clinical trial. J Immunother Cancer. 2018;6(1):7.
85. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med. 2017;377(20):1919–29.
86. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373(2):123–35.
87. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015;372(4):311–9.
88. Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016;375(19):1856–67.
89. Yau TKY, Kim T, El-Khoueiry AB, Armando S, Sangro B, Melero I, et al. Nivolumab + ipilimumab combination therapy in patients with advanced hepatocellular carcinoma: results from CheckMate 040. J Clin Oncol. 2019;37:4012.
90. Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018;378(22):2078–92.
91. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gumus M, Mazieres J, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med. 2018;379(21):2040–51.
92. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375(19):1823–33.
93. Nghiem P, Bhatia S, Lipson EJ, Sharfman WH, Kudchadkar RR, Brohl AS, et al. Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. J Clin Oncol. 2019;37(9):693–702.
94. Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro G Jr, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019;394(10212):1915–28.
95. Mehra R, Seiwert TY, Gupta S, Weiss J, Gluck I, Eder JP, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012. Br J Cancer. 2018;119(2):153–9.
96. Chen R, Zinzani PL, Fanale MA, Armand P, Johnson NA, Brice P, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol. 2017;35(19):2125–32.