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Review

Review of Immunotherapy Efficacy in Virus-associated Cancers

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Abstract

Currently, cancer is an important health problem, and virus-related infections have a large share among the factors that have been confirmed to play a role in the etiology of cancer. Until now, virus-associated cancers and nonvirus-associated cancers are treated with the same therapeutic agents. The answer to the question of whether the treatment of virus-associated tumors should be different from the treatment of other tumors has not yet been clearly answered. In addition to protective methods such as vaccination and pretransfusion serological tests, the immune system also plays an important role in eliminating the virus from the body. Besides, viruses escape from the immune system in various ways. Immunotherapies, which have been used in recent years, have brought a different dimension to cancer treatment by eliminating the inhibition of the immune checkpoint and activating T lymphocytes, thus showing an immunostimulating effect. The data showing that these agents, which are used in many types of cancer, may also be effective in virus-related cancers are increasing day by day. In this review, we aimed to evaluate the results of immunotherapies in randomized controlled trials in virus-associated cancers. Immunotherapies can play a role in many issues such as treatment of premalignant lesions and elimination of suppression or immunity after malignancy develops. As we summarized in our study, many randomized controlled clinical studies are ongoing to investigate the effectiveness of immunotherapies in virus-related cancers, and the results of these studies will answer many questions.

Keywords: Immunotherapies, immune system, malignancy, virus-associated cancers, virus infections

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Cancer is an important health problem and is one of the leading causes of death in the world. The incidence of cancer is increasing every year, and approximately 9 million people die of cancer every year.[1] About one-third of cancer deaths are due to smoking, alcohol use, obesity, and lack of physical activity.[2] Chronic infections are responsible for about one-third of cancer cases, and the most important of these are hepatitis viruses (HCV and HBV), papillomaviruses (HPV), and Helicobacter pylori infections.[3] Until the last few years, systemic chemotherapy agents have been used alongside local treatments such as surgery and radiotherapy. Although longer survival times are achieved with combined therapies, targeted therapies and immunotherapy agents have reshaped cancer treatment in recent years. Currently used immune checkpoint drugs mainly target programmed death-1 (PD-1), programmed death ligand-1 (PD-L1), and cytotoxic T lymphocyte antigen-4 (CTLA-4). Immunotherapy agents abolish immunosuppression, reactivate T cells, and stimulate the immune response. There are many immunotherapy agents used in clinical practice. Some of them are anti-PD-1 (nivolumab and pembrolizumab), anti-PD-L1 (atezolizumab, avelumab, and durvalumab), and anti-CTLA-4 (ipilimumab and tremelimumab).

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About 20% of all cancers are associated with carcinogenic viruses, and this rate is particularly high in developing countries.[3] There are 7 viruses identified as human carcinogens by the IARC.[4] These include human papillomavirus (HPV), Epstein–Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), human herpesvirus 8, human immunodeficiency virus type 1 (HIV-1), and human T cell lymphotropic virus type 1. Although all of these viruses have been identified as carcinogenic, HPV, HBV, HCV, and EBV-related cancers are detected more frequently.[5,6] Although oncogenic viruses belong to different virus families and use different strategies for cancer development, they also share many common features. One common feature is that oncogenic viruses infect host cells but do not kill them. Unlike many other disease-causing viruses, oncogenic viruses tend to cause persistent infection.[7] Another common point is that the development of virus-associated cancer can be predicted by using viral markers and the incidence of cancer can be reduced by preventing viral infection. In addition, there may be differences in treatment and prognosis between virus-associated cancers and nonvirus-associated cancers of the same organ.[8] For example, HPV positivity has been reported as a better prognostic for oral cavity cancers and cervical cancers.[8,9] On the other hand, it is known that while the response rates to sorafenib treatment are low in HCV positive or nonviral hepatocellular cancer patients, the response rates are better in HBV positive hepatocellular carcinoma (HCC) patients.[10] This suggests that immunotherapy responses may be different in patients with virus-associated cancer.

Carcinogenic viruses cause cancer development by many different mechanisms. Viral genes cause DNA damage in host cells and different mutations develop in the tumor as a result of DNA damage.[5,11] The resulting genetic instability and mutation load trigger the initiation of the carcinogenic process.[5] Although some viruses, such as HIV, are not oncogenic themselves, they inhibit the patient's immune system, disrupting the immune control and causing hypermutated malignant cells.[12] Another important way in the development of cancer with oncogenic viruses is that oncogenic viruses induce the cancer formation process by causing persistent and chronic infections. Carcinogenic viruses use different pathways to escape the immune system and increase their resistance. Immune escape mechanisms include producing anti-inflammatory cytokines, inducing regulatory T cells, and increasing the expression of immune checkpoint proteins.[3,11] Therefore, the effectiveness of anticancer treatment can be increased by removing the inhibition of the immune checkpoint and stimulating the immune system with immunotherapy agents.

Randomized controlled studies have been conducted to investigate the efficacy of immunotherapy agents in almost all tumor types. However, the relationship between virus-associated cancers and immunotherapy effectiveness has not been clearly determined. In this review, we aimed to analyze the effectiveness of immunotherapy in virus-associated and nonvirus-associated cancers by analyzing randomized controlled clinical trials in virus-associated cancers.

HPV-Associated Cancers

HPV is a small nonenveloped DNA virus that infects both the genital and oral mucosa and the basal keratinocytes of the skin. HPV can cause benign lesions such as papillomas and warts and malignant lesions such as cervical, vaginal, vulvar, anal, penile, and oropharyngeal cancers in humans. HPV-associated cancers show a better prognosis than those of the same cancers that are not related to HPV.[13] HPV is a common virus all over the world, and it has been reported that HPV is responsible for most of the cancers that develop due to infection, especially in women.[14] Despite the widespread use of multiple treatment options and the good prognosis of HPV-associated cancers, some cancers can be aggressive and difficult to treat. Therefore, HPV-associated cancers still pose a major problem and the search for effective treatment continues.

Head and neck cancers are a group of malignancies that include many subtypes, and most of them are squamous cell cancers. It has been found that 63% of oropharyngeal cancers detected each year are HPV-related.[15] For this reason, the frequency of immunotherapy administrations is increasing for squamous cell head and neck cancers (HNSCC), and many clinical trials are being conducted to investigate the effectiveness of immunotherapy for these cancers. In the KEYNOTE-012 clinical trial evaluating the safety and efficacy of pembrolizumab in patients with relapsed or metastatic HNSCC, the objective response rate (ORR) of pembrolizumab treatment was 25% (95% CI 7–52) in HPV-positive patients and 14% (95% CI 4–32) in HPV-negative patients.[16] The CheckMate 141 study evaluated the efficacy of nivolumab in patients with platinum refractory relapse or metastatic HNSCC.[17] The 1-year survival rate with nivolumab was 36%, while it was 16% for standard treatments. On the other hand, while the ORR with nivolumab was 26.2% in p16-positive patients, this rate was 20.8% in p16-negative patients. The results of both KEYNOTE-012 and CheckMate 141 show that HPV-positive patients have a higher response rate with immunotherapy agents than in HPV-unrelated HNSCCs. In addition, in the KEYNOTE-048 study, the combination of pembrolizumab and chemotherapy achieved longer survival than the cetuximab and

chemotherapy combination (13 months vs 10.7 months) in recurrent or metastatic HNSCCs.[18] In addition, in patients with p16 positive, the pembrolizumab + chemotherapy arm was found to be significantly superior to the cetuximab chemotherapy arm (HR 0.56, 95 CI 0.36–0.87). On the other hand, immunotherapy efficacy was decreased in p16-negative patients (HR 0.76, 95 CI 0.62–0.94). In the clinical trial NCT02586207, pembrolizumab therapy combined with cisplatin-based chemoradiotherapy was given in locally advanced HNSCC cases. While the ORR was 85.3% in HPV-positive patients, this rate was 78.3% in HPV-negative patients.[19]

Cervical cancer is the fourth most common cancer among women worldwide.[1] Although the incidence of HPV-associated cervical cancer has decreased with vaccination and screening programs in developed countries, it still has a significant incidence and mortality in developing countries. Standard chemoradiotherapy for cervical cancer is inadequate in a large group of patients, and the median overall survival for advanced cervical cancer is 16.8 months.[20] For this reason, it is important to develop new therapeutic approaches, and clinical studies are carried out, investigating the effectiveness of immunotherapy. The KEYNOTE-158 clinical trial investigated the efficacy of pembrolizumab in recurrent and unresectable cervical cancer.[21] The patients were given only pembrolizumab treatment, and ORR to treatment was 12.2%. Based on the results of this study, the U.S. Food and Drug Administration (FDA) has approved the use of pembrolizumab for recurrent or metastatic cervical cancer. The CheckMate 358 study evaluated the efficacy of nivolumab therapy in previously treated patients with recurrent or metastatic cervical cancer.[22] Patients with cervical, vaginal, and vulvar cancer were treated with nivolumab until progression or toxicity. The ORR was found to be 26.3% in the whole population, while the objective response was found only in patients with cervical cancer. It was observed that the responses were independent of HPV status. In the first quarter of 2022, the success of immunotherapy agents in cervical cancer has been published one after the other. In the KEYNOTE-826 study, platinum–taxane–bevacizumab therapy was combined with pembrolizumab therapy and compared with placebo in patients with recurrent or metastatic cervical cancer.[23] While the ORR was 66% in patients receiving pembrolizumab, this rate was 51% in the placebo arm. In the second-line treatment, cemiplimab and single-agent chemotherapy were compared, and the ORR rate in the cemiplimab arm was found to be statistically high (16.4% vs 6.3%).[24] In another phase III study designed in the same way, the ORR of balstilimab and zalifrelimab dual immunotherapy was found to be 25.6% in the treatment of second-line cervical cancer.[25] Although there are no data on the relationship with HPV positivity in these 3 studies in cervical cancer, considering that HPV is the most common cause of cervical cancer, it can be thought that immunotherapy would be effective in patients with HPV positivity.

Anal squamous cell carcinoma is a rare tumor and mostly develops secondary to HPV infection.[26] The standard treatment for anal squamous cell carcinoma is simultaneous chemotherapy and radiotherapy. However, treatment options are limited and 20%–30% of patients present with regional recurrence and 10%–30% with metastatic disease.[27] As more than 90% of SCCAs are HPV-related, immunotherapy is one of the possible new treatments for this rare cancer.[26] In the KEYNOTE-028 clinical trial, the ORR of pembrolizumab monotherapy in patients with anal SCC was 17% (95% CI 5–37).[28] In addition, the ORR of nivolumab in patients with metastatic anal SCC in the phase II trial NCT02314169 was 24% (95% CI 15–33).[29] No subgroup analysis of response rate with HPV infection was presented in either study. The clinical studies that resulted in HPV-associated cancers and that are still ongoing are listed in Tables 1 and 2, respectively.

EBV-Associated Cancers

EBV was the first virus shown to cause cancer in humans, and 90%–95% of all people worldwide are infected with EBV.[30] EBV-related cancers constitute 1.5% of all cancers, and EBV-related cancers are responsible for 1.8% of cancer-related deaths.[30] Although primary infection occurs in oropharyngeal epithelial cells, EBV predominantly infects B lymphocytes.[31] EBV has been found to be associated with many malignancies in humans. Some of these include Hodgkin lymphoma, Burkitt lymphoma, nasopharyngeal cancer (NPC), and gastric cancer (GC).[31] EBV-associated neoplasms occur in immunocompromised individuals as well as in immunocompetent hosts.

The cancer most closely associated with EBV infection is NPC, which is endemic to southern China.[32] The initiation of latent EBV infection in the nasopharyngeal epithelium is believed to be an early stage of NPC pathogenesis, and viral proteins are known to play important roles in promoting cancer development and progression.[33] Recent findings on pathogenesis show that targeting EBV proteins with immunotherapy may be effective in cancer treatment. In the NCI-9742 clinical trial, patients with recurrent or metastatic NPC were treated with nivolumab, and the ORR was 20.5%.[34] No statistical correlation was found between ORR and plasma EBV DNA clearance, but with the promising result of the study, trials investigating

Table 1. Published clinical trials evaluating ICIs in HPV-associated cancers

Clinical trial	Phase	Stage	Comparison	Results
HNSCC				
KEYNOTE-012[16]	1b	Recurrent or metastatic	Pembrolizumab monotherapy	HPV positive patients ORR 25% HPV negative patients ORR 14%
CheckMate 141[17]	3	Recurrent and platinum refractory	*Nivolumab monotherapy *Standard (methotrexate, docetaxel, or cetuximab)	1-year survival rate in Nivolumab arm 36% Standard therapy arm 16%
KEYNOTE-040[47]	3	Recurrent and platinum refractory	*Pembrolizumab monotherapy *Standard (methotrexate, docetaxel, or cetuximab)	1-year survival rate in Pembrolizumab arm 37% Cetuximab arm 26%
KEYNOTE-048[48]		Recurrent	*Pembrolizumab monotherapy *Pembrolizumab + cisplatin and 5 FU *Cetuximab + cisplatin and 5 FU	Overall survival Pembrolizumab + CT 13 m Cetuximab + CT 10.7 m Pembrolizumab monotherapy superior to cetuximab + CT (CPS > 1)
EAGLE[49]	3	Recurrent	*Durvalumab monotherapy *Durvalumab + tremelimumab *Standard chemotherapy	1-year survival rate in *Durvalumab monotherapy 37% *Durvalumab + tremelimumab 30% *Standard 30%
GORTEC 2015-01[50]	2	Locally advanced, platinum ineligible	*Pembrolizumab + RT *Cetuximab + RT	Locoregional control rate *Pembrolizumab + RT 60% *Cetuximab + RT 59%
NCT02586207[51]	1b	Locally advanced	Pembrolizumab + cisplatin + RT	ORR HPV positive HNSCC ORR 85.3% HPV negative HNSCC ORR 78.3%
Cervical cancer				
KEYNOTE-158[21]	2	Recurrent/metastatic	Pembrolizumab monotherapy	ORR %12
KEYNOTE-826[23]	3	Recurrent/metastatic	*Pembrolizumab + standard CT *Standard CT	ORR *Pembrolizumab + standard CT 66% *Standard CT 51%
CheckMate 358[22]	1/2	Recurrent/metastatic	Nivolumab Nivolumab + Ipilimumab	ORR Nivolumab 26% Nivolumab-Ipilimumab 40%
RaPIDS[25]	2	Recurrent/metastatic	Balstilimab + zalifrelimab	ORR 26%
Cemiplimab[24]	3	Recurrent/metastatic	*Cemiplimab monotherapy *Standard chemotherapy	ORR *Cemiplimab %16 *Standard CT %6
Anal cancer				
NCI9673[29]	2	Recurrent/metastatic	Nivolumab monotherapy	ORR 24 %
KEYNOTE-28[28]	1b	Locally advanced/metastatic	Pembrolizumab monotherapy	ORR 17 %

ORR: Objective response rate.

the effectiveness of immunotherapy in the treatment of NPC have increased. In the KEYNOTE-028 clinical trial, 27 patients with PD-L1-positive recurrent or metastatic NPC were treated with pembrolizumab.[35] Partial response was observed in 7 patients, stable disease was observed in 14 patients, and the ORR was 25.9% (95% CI 11.1–46.3). One of the most recent studies, CAPTAIN-1st, is a multicenter, randomized, double-blind phase III study comparing gemcitabine plus cisplatin (GP) and GP plus camrelizumab combination.[36] The median progression-free survival (mPFS) was 6.9 months (95% CI 5.9–7.3) in the GP arm compared with 9.7 months (95% CI 8.3–11.4) in the cam-

Table 2. Ongoing clinical trials evaluating ICIs in HPV-associated cancers

Clinical trial	Phase	Stage	Comparison	Results
HNSCC				
JAVELIN HN100	III	Locally advanced (Stages III–IV)	*Avelumab + chemoradiotherapy *Chemoradiotherapy	According to the interim analysis, it was determined that the study was not beneficial and the study was terminated early
KEYCHAIN	II	Locally advanced	*Pembrolizumab + RT *Chemotherapy	Waiting
HN-005	II/III	Stages I–III p16+	*Nivolumab + RT *Cisplatin + RT	Waiting
HN-004	II/III	Locally advanced, platinum ineligible	*Durvalumab + RT *Cetuximab + RT	Waiting
Cervical cancer				
CALLA	III	Locally advanced	*Durvalumab + cisplatin + RT *Cisplatin + RT	Waiting
NCT02635360	II	Locally advanced	*Pembrolizumab + cisplatin + RT *Cisplatin + RT	Waiting
BEATcc	III	Recurrent/metastatic	*Atezolizumab + standard CT *Standard CT	
SKYSCRAPER-04	II	Recurrent/metastatic	Tiragolumab + atezolizumab	Waiting

relizumab group. In the JUPITER-02 phase III study, the results of which are shown in ASCO-2021, the efficacy of toripalimab treatment in combination with gemcitabine–cisplatin chemotherapy was evaluated.[37] The mPFS was found to be 11.7 months in the patients who received toripalimab, and 8.0 months in the group that was not administered. Considering the relationship between viral load and treatment responses, it is understood that patients with EBV DNA positive from camrelizumab treatment respond more than those with negative EBV DNA (HR 0.45 vs HR 0.57). Also in the subgroup analysis of the JUPITER study, the calculated HR for the contribution of toripalimab to PFS was 0.57 for those with EBV DNA copies < 2000 and HR 0.46 if EBV DNA > 2000 copies. The results of these studies suggest that the use of immunotherapy agents in combination with standard GP chemotherapy may be standard for recurrent or metastatic NPC.

Although the association between EBV and malignancy was initially detected with Burkitt lymphoma, subsequent developments have shown that it may also play a role in the pathogenesis of other lymphomas. In a clinical trial investigating the efficacy of pembrolizumab treatment in recurrent or refractory NK/T-cell lymphoma, 7 patients were given 7 cycles of pembrolizumab and followed up for 6 months.[38] As a result of the study, complete response was observed in 5 patients (71.4%) and molecular remission (undetectable EBV DNA) was found in 2 patients. This study has shown that pembrolizumab can be a potent therapeutic agent for NK/T-cell lymphomas unresponsive to L-asparaginase therapy. The efficacy of pembrolizumab in EBV-positive and EBV-negative patients was investigated in 30 patients diagnosed with resistant/recurrent non-Hodgkin lymphoma.[39] Among the EBV-positive patients (n=15), 7 patients (46.7%) were found to respond to treatment and these included subtypes such as NK/T-cell lymphoma and primary mediastinal B-cell lymphoma. None of the EBV-negative patients (n=15) had a partial or objective response to pembrolizumab, and these included subtypes such as diffuse large B-cell lymphoma and T-lymphoblastic lymphoma. In addition, PD-L1 expression was found to be significantly higher in EBV-positive (56%) than EBV-negative NHL (11%) in the study (p<0.001). Due to the high expression of PD-L1, it is estimated that immunotherapy may be more effective in EBV-positive lymphomas.

GC is one of the most common cancer types in the world, and EBV-associated GC accounts for 10% of all molecular subtypes.[40] Immunotherapy data in patients with EBV-associated metastatic GC are conflicting. In patients with EBV-positive GC treated with pembrolizumab in the second or subsequent line of treatment, the ORR was 100%, compared with 25% with nivolumab.[41,42] The clinical studies that resulted in EBV-associated cancers and that are still ongoing are listed in Tables 3 and 4, respectively.

Table 3. Published clinical trials evaluating ICIs in EBV-associated cancers

Clinical trial	Phase	Stage	Comparison	Results
Nasopharynx cancer				
NCI-9742[34]	II	Recurrent/metastatic	Nivolumab monotherapy	ORR 20.5%
KEYNOTE-28[52]	Ib	Recurrent/metastatic	Pembrolizumab monotherapy	ORR 26%
CAPTAIN-1st[36]	III	Recurrent/metastatic	*Camrelizumab + standard CT *Standard CT	Progression-free survival *Camrelizumab + standard CT 9.7 m *Standard CT 6.9 m
JUPITER-02[37]	III	Recurrent/metastatic	*Toripalimab + standard CT *Standard CT	Progression-free survival *Toripalimab + Standard CT 11.7 m *Standard CT 8.0 m
NCT02875613[53]	II	Recurrent/metastatic	Avelumab monotherapy	Terminated
Lymphoma				
Asia Lymphoma Study Group[38]	Retrospective	Relapsed/refractory NK /T cell lymphoma	Pembrolizumab monotherapy	ORR 71%
Kim et al.[39]	Retrospective	Relapsed/refractory NHL	Pembrolizumab monotherapy	ORR 23 %
Gastric cancer				
NCT02589496[41]	II	Metastatic	Pembrolizumab monotherapy	ORR 100%
Mishima et al.[42]	Retrospective	Metastatic	Nivolumab monotherapy	ORR 25 %

ORR: Objective response rate.

Table 4. Ongoing clinical trials evaluating ICIs in EBV-associated cancers

Clinical trial	Phase	Stage	Comparison	Results
Nasopharynx cancer				
NCT02488759	I/II	Recurrent/metastatic	Nivolumab + ipilimumab	Waiting
NCT03267498	II	Stages II–IVB disease	Nivolumab + chemoradiation	Waiting
NCT02834013	II	Recurrent/metastatic	Nivolumab + ipilimumab	Waiting
NCT03427827	III	Locally advanced	After completion of chemoradiation *Camrelizumab *Best supportive care	Waiting
NCT03813394	I/II	Recurrent/metastatic	Pembrolizumab±bevacizumab	Waiting
Lymphoma				
NCT03258567	II	EBV-positive lymphoproliferative disease/NHL	Nivolumab monotherapy	Waiting
NCT03015896	I/II	Relapsed/refractory NHL or HL	Nivolumab + lenalidomide	Waiting
NCT02973113	I	Relapsed/refractory EBV + lymphoma	Nivolumab + EBV-specific cytotoxic T-lymphocytes	Completed but results not announced
NCT03160079	I/II	Relapsed/refractory B-cell ALL	Pembrolizumab + blinatumomab	Waiting
NCT02950220	I	Relapsed/refractory NHL	Pembrolizumab + ibrutinib	Completed but results not announced
Gastric cancer				
NCT03257163	II	EBV-positive gastric cancer – adjuvant therapy	Pembrolizumab + capecitabine + radiotherapy	Waiting
NCT03735290	I/II	Advanced gastric cancer	Pembrolizumab + ilixadencel	Waiting

Hepatitis B-Associated and Hepatitis C-Associated Cancers

Chronic HBV and chronic HCV infections are closely related to HCC development. Millions of people worldwide are chronically infected with HBV, and half of HCC cases are associated with chronic HBV infection. During chronic infection, recurrent liver inflammation as a result of the host immune response increases the hepatocyte turnover rate by causing liver fibrosis and cirrhosis and leads to the develop-

ment of HCC by causing mutations to accumulate. HBV integration into host cells and encoding of HBV oncoproteins (e.g., HBx and truncated preS2/S proteins) also induce HCC development. Although important breakthroughs such as HBV vaccines and antiviral therapies have been made to prevent the development of virus-associated HCC, HCC treatment is still an important problem and the effectiveness of immunotherapy in treatment is being investigated. Hepatitis B or C positivity was determined as an exclusion criterion in all phase II–III studies, with the only exception being HCC studies.

A multicenter, randomized, phase I/II study, CheckMate 040 evaluated the efficacy and safety of nivolumab and ipilimumab in patients with advanced HCC who had been previously treated with sorafenib.[43] In this study, 148 patients participated and they were divided into three arms. Patients in arm A received 1 mg/kg nivolumab plus 3 mg/kg ipilimumab every 3 weeks (4 doses), followed by 240 mg nivolumab every 2 weeks; those in arm B received 3 mg/kg nivolumab plus 1 mg/kg ipilimumab every 3 weeks (4 doses), followed by 240 mg nivolumab every 2 weeks; those in arm C received nivolumab 3 mg/kg every 2 weeks plus 1 mg/kg ipilimumab every 6 weeks. The ORR was 32% in arm A, 27% in arm B, and 29% in arm C. Patients were evaluated separately as HBV or HCV uninfected, HBV infected, HCV infected and overall survival in arm A was 22.2, 22.8, and 14.9 months; 11.8, 12.1, and 16.1 months in arm B; 7.4, 9.6, and 33.0 months in arm C, respectively. As a result of the trial, the FDA approved nivolumab as a second-line treatment for liver cancer after sorafenib failure. In another study, patients with unresectable HCC were given a combination of atezolizumab and bevacizumab (n=336) or sorafenib (n=165), and the two groups were compared.[44] In the atezolizumab-bevacizumab arm, the overall 12-month survival rate was 67.2% and the mPFS was 6.8 months; 12-month survival in the sorafenib arm was 54.6% and mPFS was 4.3 months. In another clinical trial, tremelimumab and durvalumab combination or monotherapies were given to patients with unresectable HCC.[45] The ORR was 24.0% in the group receiving high-dose (300 mg) tremelimumab and durvalumab combination, 10.6% in the group receiving durvalumab monotherapy, 7.2% in the group receiving tremelimumab monotherapy, and 9.5% in the group receiving low-dose (75 mg) tremelimumab plus durvalumab combination. The median survival was 18.7 months, 13.6 months, 15.1 months, and 11.3 months in these groups, respectively. Accordingly, high-dose tremelimumab and durvalumab combination therapy was found to be more effective than the others. Another multicenter, randomized phase III study (CheckMate 459) compared first-line nivolumab (n=371) monotherapy with sorafenib (n=372) monotherapy in advanced HCC patients.[46] The median survival was 16.4 months in patients receiving nivolumab, compared with 14.7 months in the group receiving sorafenib. The ORR was 15% in the nivolumab arm and 7% in the sorafenib arm. In the nivolumab group, the response rate was 19% in HBV-infected patients, compared with 8% in the sorafenib arm. Likewise, in HCV-positive patients, the ORR was found to be 17% with nivolumab and 7% with sorafenib. In addition, in the subgroup analysis of the study, the hazard rate (HR) was found to be 0.71 and 0.77, respectively, in those infected with HBV and HCV, while the HR was calculated as 0.95 in the uninfected. According to the study, first-line nivolumab treatment did not significantly improve overall survival compared with sorafenib, but according to the subgroup analysis of the study, nivolumab was more effective in chronic HBV- and HCV-infected patients than in uninfected patients. The clinical studies that resulted in HBV/HCV-associated cancers and that are still ongoing are listed in Tables 5 and 6, respectively.

Conclusion

One of the greatest achievements in cancer therapy over the past decade has been the introduction of T-cell-targeted immune modulators that block the CTLA-4 and PD-1 or PD-L1 immune checkpoints. Immunotherapy agents are now used as a first- or second-line of treatment for approximately 50 types of cancer, either as monotherapy or in combination with chemotherapies. There are more than 3000 active clinical studies evaluating T cell modulators, and they account for about two-thirds of all oncology studies. In virus-associated cancers, carcinogenic virus DNA interacts with host DNA by inducing DNA damage response and increases the mutation rate, accelerating the acquisition of oncogenic chromosomal changes in host cells. At the same time, oncogenic viruses increase the inhibition of the immune system by interacting with the immune checkpoints and thus facilitate the proliferation of hypermutated cells. Immunotherapies might play a role in many issues such as prevention of viral infections, treatment of premalignant lesions, and elimination of suppression on immunity after malignancy develops. As we emphasize in our study, many randomized controlled clinical studies are ongoing to investigate the effectiveness of immunotherapies in virus-related cancers, and the results of these studies will answer many questions.

Table 5. Published clinical trials evaluating ICIs in HBV and HCV-associated hepatocellular cancer

Clinical trial	Phase	Stage	Comparison	Results
Hepatocellular cancer				
CheckMate 040[43]	I/II	Advanced HCC	*Arm A: nivolumab (3 mg/kg) + ipilimumab (1 mg/kg)	ORR 31%
			*Arm B: nivolumab (1 mg/kg) + ipilimumab (3 mg/kg)	ORR 27%
			*Arm C: nivolumab (240 mg) + ipilimumab (3 mg/kg)	ORR 29%
IMBRAVE 150[44]	III	Unresectable HCC	*Atezolizumab + bevacizumab *Sorafenib	1-year survival rate in Atezolizumab + bevacizumab 67% Sorafenib 55%
NCT02519348[45]	I/II	Unresectable HCC	Tremelimumab + durvalumab	ORR 24%
CheckMate 459[46]	III	Unresectable HCC	Nivolumab vs sorafenib	ORR Nivolumab 15% Sorafenib 7%
RESCUE[54]	II	Advanced HCC	Camrelizumab + apatinib	ORR 34 %
NCT03006926[55]	Ib	Unresectable HCC	Pembrolizumab + lenvatinib	ORR 46 %
KEYNOTE-240[56]	III	After sorafenib failure	Pembrolizumab monotherapy	ORR 18 %

ORR: Objective response rate.

Table 6. Ongoing clinical trials evaluating ICIs in HBV and HCV-associated hepatocellular cancer

Clinical Trial	Phase	Stage	Comparison	Results
Hepatocellular cancer				
KEYNOTE-394	III	Advanced HCC	After standard therapy *Pembrolizumab *Placebo	Waiting
RATIONALE 301	III	Unresectable HCC	*Tislelizumab *Sorafenib	Waiting
HIMALAYA	III	Unresectable HCC	*Durvalumab + tremelimumab *Durvalumab *Sorafenib	Waiting
LEAP-002	III	Unresectable HCC	*Pembrolizumab + lenvatinib *Lenvatinib	Waiting
COSMIC-312	III	Advanced HCC	*Atezolizumab + cabozantinib *Sorafenib	Waiting
EMERALD-1	III	Advanced HCC	*Durvalumab + bevacizumab + TACE *Durvalumab + TACE *TACE	Waiting
CheckMate 9DX	III	Resectable HCC	*Nivolumab + curative resection/RFA *Curative resection/RFA	Waiting
EMERALD-2	III	Resectable HCC	*Durvalumab + bevacizumab + curative resection/RFA *Durvalumab + curative resection/RFA *Curative resection/RFA	Waiting

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