Immuno-Oncology in Hepatocellular Carcinoma: 2017 Update

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Keywords

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Abstract

Clinical trials are currently ongoing to evaluate the utility of antibodies against programmed cell death 1 (PD-1), programmed cell death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) as monotherapy or combination therapy in patients with hepatocellular carcinoma (HCC). Results of combination treatment with the anti-PD-L1 antibody durvalumab and the anti-CTLA-4 antibody tremelimumab in HCC were presented at the 2017 annual meeting of the ASCO (American Society of Clinical Oncology). Response rates were 25% in all 40 patients and 40% in the 20 uninfected patients, both of which are encouraging. Transcatheter arterial chemoembolization and radiofrequency ablation can activate tumor immunogenicity by releasing tumor-associated antigen and by inducing the migration of cytotoxic T lymphocytes to small intrahepatic metastatic nodules. Subsequent administration of anti-PD-1 antibody could control these small intrahepatic metastatic nodules. In a nonclinical study, the combination of pembrolizumab and lenvatinib inhibited the cancer immunosuppressive environments induced by tumor-associated macrophages and regulatory T cells. This, in turn, decreased the levels of TGF- β and IL-10, the expression of PD-1, and the

inhibition of Tim-3, triggering anticancer immunity mediated by immunostimulatory cytokines such as IL-12. Studies such as these may provide insight into the appropriate molecular targeted agents to be used with immune checkpoint inhibitors.

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Introduction

Clinical trials are currently ongoing to evaluate the utility of antibodies against programmed cell death 1 (PD-1), programmed cell death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), as monotherapy or combination therapy, in patients with hepatocellular carcinoma (HCC). This article reviews current knowledge of immune checkpoint inhibitors and trends in clinical trials for HCC.

Theoretical Basis of Enhanced Tumor Immunoreactivity by Immune Checkpoint Inhibitors

During carcinogenesis, the transformation of cancer cells is associated with recognition of tumor-associated antigens (TAAs) by a group of proteins called the major histocompatibility complex (MHC) on the surface of antigen-presenting cells. These cells subsequently migrate to

Fig. 1. T cell-mediated cancer immunity including priming phase at the lymph nodes and effector phase at the cancer microenvironment.

Fig. 2. The immune system is capable of eliminating tumor cells through 7 steps. Adapted from Chen and Mellman [1].

lymph nodes, where they present TAAs to T cell receptors (TCR) on the surface of immature T cells (signal 1). Immature T cells cannot be activated by the binding between TAA and TCR (signal 1), but require a co-stimulatory signal (signal 2). This signal is generated when B7 proteins (CD80/B7-1 and CD86/B7-2) on antigen-presenting cells bind to CD28 on immature T cells, inducing the differentiation of these T cells into CD8⁺ T cells (priming phase). Subsequently, activated T cells migrate through the blood-

stream to the tumor microenvironment, where they recognize TAAs presented by the MHC on tumor cells and begin to attack the cells by releasing perforin and granzyme (effector phase) (Fig. 1). This process has been called the conventional cancer immunity cycle (Fig. 2) [1].

Although T cells are effective initially, they lose their effect relatively quickly. Previous attempts to enhance anticancer immunity have involved the activation of immune-stimulatory mechanisms by various modalities, in-

Fig. 3. There are 2 immune regulatory co-signals: stimulatory and inhibitory co-signals. These are called immune checkpoints. Since affinity of CTLA-4 to B7 is 10 times stronger than that of CD28, second inhibitory co-signal induces T cell in activation.

cluding peptide, dendritic cell, cytokine, and lymphokine-activated killer cell therapy. These attempts, however, seldom produced satisfactory results, largely because the body's innate immune system, which negatively regulates immune responses (immune evasion mechanism), was incompletely understood. In reality, attempts to progressively enhance immune responses reinforce an immune system that negatively regulates immune response in reaction to positive regulation. These theoretical and practical reasons may explain the failure of previous studies that employed immunostimulatory therapy alone.

In humans, immune escape in cancer is mediated largely by two mechanisms: one in the lymph nodes and the other in the tumor microenvironment.

Cancer Immune Escape and Inhibitors

CTLA-4 Pathway and Inhibitors

The CTLA-4 pathway regulates the proliferation of activated lymphocytes, primarily in the lymph nodes. CTLA-4 is constitutively expressed by regulatory T cells

(Tregs), but is also expressed transiently by other types of T cells during the early phase of activation (within 24–48 h). Because CTLA-4 has a ≥ 10 -fold greater affinity to B7 than does CD28, the affinity of CTLA-4 to T cells activated via the B7/CD28 pathway (stimulatory signal 2) is ≥ 10 times that of CD28. Thus, CTLA-4 binds to B7-1/B7-2 by competing with CD28 and transmits inhibitory signal 2 to the T cell. Under normal physiological conditions, CTLA-4 terminates T cell activity, which is no longer needed to regulate excessive immune response mediated by T cells. However, in cancer, CTLA-4 suppresses the proliferation (activation and production) of T cells that have undergone TAA recognition and differentiation (Fig. 3, 4).

The immunosuppressive mechanism underlying T cell activation in the lymph nodes can be counteracted by antibodies against CTLA-4. The first use of anti-CTLA-4 antibody in cancer treatment was reported in 1996, with this antibody successfully eliminating tumor cells in mice.

As described above, CTLA-4 is expressed at high levels by Tregs. Accordingly, one of the actions of anti-CTLA-4 antibody may be to downregulate Tregs in the tumor mi-

Fig. 4. T cell inactivation and cancer immune escape by CTLA-4, PD-1, and PD-L1. As a result, T cell is failed to be activated at the lymph node.

Fig. 5. Immune regulatory co-signaling (immune checkpoints: stimulatory and inhibitory) in cancer microenvironment. At the tumor microenvironment, cytotoxic T cell is inactivated by secondary inhibitory signal through the PD-1/PD-L1 pathway by IFN γ produced by transient activation of CTL.

Fig. 6. Cancer attack by CTLs activated by the immune checkpoint inhibitors anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies. By the administration of anti-CTLA-4, anti-PD-1 and anti-PD-L1 antibodies, T cell activation and effective cancer attack by activated T cell are restored.

croenvironment. Clinical studies are currently underway to aggressively evaluate the efficacy of the anti-CTLA-4 antibodies ipilimumab and tremelimumab.

The PD-1/PD-L1 Pathway and Its Inhibitors

PD-1, a receptor for co-inhibitory signals, is expressed by T cells and B cells, and in bone marrow, and inhibits antigen-specific activation of T cells by binding to PD-L1/PD-L2. PD-L2 is expressed only by dendritic cells, whereas PD-L1 is expressed by dendritic cells and various tissue types, including blood vessels, heart, lungs, and placenta.

PD-1 is barely detected in normal mice or in peripheral blood of healthy humans, whereas it is expressed in the late phase of T cell activation in response to infection and inflammation. Under these conditions, PD-1 is expressed at particularly high levels by effector T cells circulating in peripheral blood.

In contrast to PD-1, PD-L1 is expressed constitutively in peripheral tissues under normal physiologic conditions. Upon induction of an immune response, almost all immunocompetent cells, including T cells and B cells, start to express PD-L1. In addition, most cancer cells express PD-L1 through a mechanism described below.

By contrast, the expression and function of PD-L2 are limited because it is expressed only by antigen-presenting cells and is involved in the activation of T cells in the lymph nodes. This may explain why the effect of PD-L2 is thought to play a limited role in cancer immunity, whereas anti-PD-1 antibody and anti-PD-L1 antibody are comparably effective.

Upon recognition by surface TCR of tumor antigens presented by the MHC, activated T cells transmit a signal to attack cancer cells by releasing perforin or granzyme and simultaneously delivering cytokines, mainly interferon γ , to cancer cells. In response to this stimulation, cancer cells express PD-L1, which binds to PD-1 as a defense mechanism. This results in the transmission of inhibitory signals to cytotoxic T lymphocytes, thereby reducing their potency (immune evasion or immune tolerance) (Fig. 5).

If anti-PD-1 antibody is administered at this point, it will unlock the negative regulation of the immune response, and enable recovery of the ability to attack cancer cells (Fig. 6). That is, unlike conventional chemotherapy or molecular targeted therapy, antibody therapy improves the potency of attack on cancer cells by restoring

Table 1. Immune checkpoint inhibitors in HCC clinical trials

Target cell	Target molecule	Development code	Drug name	Commercial name	Antibody	Company
T lymphocyte	PD-1	BMS-36558 ONO-4538	Nivolumab	Optivo	Fully human IgG4 antibody	ONO/BMS
	PD-1	MK-4375	Pembrolizumab	Keytruda	Humanized IgG4 antibody	Merck
Tumor cell	PD-L1	MPDL3280A	Atezolizumab	Not yet approved	Fully humanized IgG1 antibody	Roche
	PD-L1	MEDI4736	Durvalumab	Not yet approved	Humanized IgG1 antibody	AstraZeneca
	PD-L1	MSB-0010718C	Avelumab	Not yet approved	Humanized IgG1 antibody	Merck-serono
T lymphocyte	CTLA-4	BMS-734016	Ipilimumab	Yervoy	Fully humanized IgG1 antibody	BMS Medarex
	CTLA-4	MEDI1123	Tremelimumab	Not yet approved	Fully humanized IgG2 antibody	AstraZeneca MedImmune

the function of the innate anticancer immune system, a powerful and precise weapon against cancer [2–13]. Anti-PD-L1 antibody has similar effects [14]. In addition, PD-L1 is reported to be a biomarker that can predict the effect of anti-PD-1 antibody [15]. However, some patients with tumors that do not express PD-L1 have also been found to benefit from anti-PD-1 antibody.

Development and a Trend of Immune Checkpoint Inhibitors for HCC

Interim results of the phase I/II CheckMate 040 clinical trial of the anti-PD-1 antibody nivolumab in patients with HCC were reported at the 2015 annual meeting of the American Society of Clinical Oncology (ASCO), held in Chicago, IL, USA [16]. Subsequent study outcomes were presented at the ASCO meetings in 2016 and 2017, and the results of the trial were published in *The Lancet* [17]. Based exclusively on these study outcomes, the United States Food and Drug Administration approved nivolumab as second-line treatment agent for HCC in September 22, 2017.

The findings of the dose escalation phase of this phase I/II trial confirmed the safety of nivolumab, at a dose of 3 mg/kg, in HCC patients infected with hepatitis C virus (HCV) or hepatitis B virus (HBV) infection, and at doses up to 10 mg/kg in HCC patients without infection. Moreover, the effectiveness and safety of this agent were evaluated in the 214 patients in the dose escalation and dose

expansion cohorts. Among the 144 (67%) patients with extrahepatic metastases and the 63 (29%) with vascular invasion, 42 (20%) showed a favorable response to nivolumab, including 3 patients who achieved complete response (CR). Also, disease progression was suppressed in 138 of the 214 (64%) patients, and the 9-month survival rate was as high as 74%. These results are considered highly promising, especially because this group of patients had highly advanced HCC.

The waterfall plots show comparable tumor-reducing effects of nivolumab in 3 types of patients, patients without viral hepatitis, whether untreated with or intolerant to sorafenib or progressing on sorafenib, and those infected with HBV or HCV infection, although the effect of nivolumab appeared to be slightly weaker in the HBV group. Some patients began to respond to this drug within 3 months of first administration, with responses being durable for a long period of time. The spider plots also show that this effect was durable not only in patients who achieved CR or partial response, but also in patients with stable disease. However, the drug was ineffective in 30–40% of these patients, with some showing rapid exacerbation of disease, suggesting that this may be the limit of monotherapy.

The 3 patients who achieved CR did so during the early phase of treatment (3–10 months) and currently remain disease-free, including one each for ≥ 25 months and ≥ 33 months. Similarly, most patients with partial response and stable disease have maintained the disease state, with few developing progressive disease due to the

Table 2. Immune checkpoint inhibitors: ongoing trials

Drug	Trial name	Clinicaltrials.gov No.	Company	Phase	Subjects, n	Line of therapy	Design	Endpoint	Status
Nivolumab Nivolumab (PD-1 Ab)/ Ipilimumab (CTLA-4 Ab)	CheckMate 040	NCT01658878	BMS/ONO	I/II	42	1 L/2 L	cohort 1: dose escalation	DLT/ MTD	completed
	CheckMate 040	NCT01658878	BMS/ONO	I/II	214	1 L/2 L	cohort 2: dose expansion	ORR	completed
	CheckMate 040	NCT01658878	BMS/ONO	I/II	200	1 L	cohort 3: nivolumab vs. sorafenib	ORR	completed
	CheckMate 040	NCT01658878	BMS/ONO	I/II	120	2 L	cohort 4: nivolumab + ipilimumab	safety / tolerability	completed
	CheckMate 040	NCT01658878	BMS/ONO	I/II	–	1 L	cohort 5: nivolumab (Child-Pugh B)	ORR	recruiting
	CheckMate 040	NCT01658878	BMS/ONO	I/II	–	1 L	cohort 6: nivolumab + cabozantinib	ORR	recruiting
	CheckMate 040	NCT01658878	BMS/ONO	I/II	–	1 L	cohort 7: nivolumab + ipilimumab + cabozantinib	ORR	recruiting
	CheckMate 459	NCT02576509	ONO	III	726	1 L	nivolumab vs. sorafenib	OS	completed
Pembrolizumab Pembrolizumab (PD-1 Ab)	KEYNOTE-224	NCT02702414	MSD	II	100	2 L	pembrolizumab (1 arm)	ORR	completed
Pembrolizumab (PD-1 Ab)	KEYNOTE-240	NCT02702401	MSD	III	408	2 L	pembrolizumab vs. placebo	PFS/OS	recruiting
Durvalumab Durvalumab (PD-L1 Ab)/ Tremelimumab (CTLA-4 Ab)	–	NCT02519348	AstraZeneca	II	144	1 L/2 L	durvalumab (arm A) tremelimumab (arm B) durvalumab + tremelimumab (arm C)	safety/ tolerability	recruiting
Durvalumab + Tremelimumab	–	NCT028211754	AstraZeneca	I/II	–	TACE/RFA	1 arm	safety/ tolerability	recruiting
MSBoo11359C (PD-L1 Ab + TGFB Trap)	–	NCT02699515	Merck-serono	I	–	1L	1 arm	safety/ tolerability	recruiting

DLT, dose-limiting toxicity; MTD, maximum tolerated dose; ORR, objective response rate; TTP, time to progression; OS, overall survival; PFS, progression-free survival.

development of drug tolerance. Accordingly, the treatment efficacy of the anti-PD-1 antibody, nivolumab has been sustained (durable response) in patients with HCC, similarly to findings in other types of cancer. This treatment outcome is typical of immune checkpoint inhibitors, and thus, deserves attention. It should also be noted that, despite nivolumab treatment being terminated a few months after the 2 above patients attained CR, both have continued to maintain CR to date. Furthermore, the interim results presented at the 2015 annual meeting of

ASCO included a patient with HCC who initially had innumerable tumors in both lobes, all of which disappeared after 6 weeks of treatment as well as showing a reduction in the α -fetoprotein level from 21,000 to 283 ng/mL. Another HCC patient initially had a tumor measuring ≥ 10 cm in diameter, but this tumor shrunk dramatically to about 2 cm after 48 weeks of treatment. Although liver damage was the most worrisome anticipated grade 3–4 treatment-related side effect, only 9 patients (4%) developed elevated aspartate aminotransferase and only 6 (3%)

Fig. 7. Future direction of treatment strategy with immune checkpoint inhibitors is a combination therapy with other check point inhibitor/stimulators, tyrosine kinase inhibitors (TKIs), transarterial chemoembolization (TACE) and resection or ablation. RFA, radiofrequency ablation; HAIC, hepatic arterial infusion chemotherapy.

developed elevated alanine aminotransferase, rates comparable to those observed in patients with other types of cancer. Furthermore, severe liver damage associated with viral hepatitis was not observed.

In summary, (1) the safety profile of monotherapy with the anti-PD-1 antibody, nivolumab was satisfactory in patients with HCC, as in other types of cancer; (2) nivolumab could be used safely in HCC patients infected with HBV or HCV; and (3) nivolumab had a remarkably high response rate as an immunotherapeutic agent with long-lasting efficacy. The durable response of nivolumab was comparable among different cohorts (patients without viral hepatitis and those infected with HBV or HCV) regardless of drug dose or etiology.

Follow-up results presented at the 2017 annual meeting of ASCO showed that the median overall survival was 28.6 months in the sorafenib-naïve group and 15.6 months in the sorafenib-experienced group, both of which are considered astounding [18].

Other Currently Ongoing Clinical Trials

Table 1 shows immune checkpoint inhibitors that are currently being evaluated in patients with HCC. At present, 5 cohorts are being evaluated in the phase I/II Check-

Mate 040 study: a dose escalation cohort (cohort 1), a dose expansion cohort (cohort 2), a randomized comparative trial with sorafenib (cohort 3), a cohort consisting of patients concurrently treated with nivolumab and the CTLA-4 antibody ipilimumab (cohort 4), and a cohort of patients with Child-Pugh class B liver function (cohort 5) (Table 2).

The results of the phase I/II CheckMate 040 study have led to the design of a phase III clinical trial directly comparing sorafenib and nivolumab, a trial currently underway. Another trial is evaluating the efficacy of the anti-PD-1, pembrolizumab as second-line therapy after sorafenib failure. Early approval of either or both of these anti-PD-1 antibodies nivolumab and pembrolizumab is anxiously awaited.

Compared with anti-PD-1 antibody, the side effects of anti-CTLA-4 antibody tend to be slightly more severe in patients with HCC [19].

Combination Therapy with Immune Checkpoint Inhibitors

Antibody therapy against PD-L1 and CTLA-4, in addition to PD-1, appears promising as immunotherapy for HCC. Indeed, studies evaluating combination therapy

Table 3. Phase I/II combination therapy with durvalumab (PD-L1 Ab) and tremelimumab (CTLA-4 Ab) in HCC

Investigator-assessed response	HBV+ (n = 11)	HCV+ (n = 9)	Uninfected (n = 20)	All (n = 40)
Confirmed ORR (all PR), % (95% CI)	0 (0.0–28.5)	11.1 (0.3–48.2)	30.0 (11.9–54.3)	17.5 (7.3–32.8)
CR + PR (confirmed + unconfirmed), % (95% CI)	9.1 (0.2–41.3)	11.1 (0.3–48.2)	40.0 (19.1–63.9)	25.0 (12.7–41.2)
CR + PR + SD ≥16 weeks (DCR16), % (95% CI)	45.5 (16.7–76.6)	44.4 (13.7–78.8)	70.0 (45.7–88.1)	57.5 (40.9–73.0)

Adapted from Kelley et al. [23]. HCC, hepatocellular carcinoma; ORR, objective response rate; PR, partial response; CR, complete response; SD, stable disease, DCR, disease control rate.

Table 4. Combination trials of immune checkpoint inhibitors with TKIs in HCC

Phase	Target	Agent	Company	Trial No.
Ib/II	PD-1 + TGF- β receptor I	nivolumab + galunisertib (LY2157299)	Lilly	NCT02423343
I	PD-1 + multikinase	pembrolizumab + lenvatinib	Eisai	NCT03006926
I	PD-1 + multikinase	pembrolizumab + nintedanib	Gustave Roussy	NCT02856425
I	PD-1 + multikinase	PDR001 + sorafenib	Novartis	NCT02988440
I/II	PD-1 + c-Met	PDR001 + capmatinib (INC280)	Novartis	NCT02795429
I	PD-L1 + VEGF	durvalumab + ramucirumab	Astra Zeneca	NCT02572687
I/II	PD-1 + VEGF	nivolumab + cabozantinib	BMS	NCT01658878
I/II	PD-1 + CTLA-4 + VEGF	nivolumab + ipilimumab + cabozantinib	BMS	NCT01658878

TKIs, tyrosine kinase inhibitors; HCC, hepatocellular carcinoma.

with multiple immune checkpoints such as anti-PD-1 antibody plus anti CTLA-4 antibody, are currently underway (Fig. 7). This combination is very effective in patients with malignant melanoma [20, 21], and is being studied in patients with HCC [22]. A rationale for combination therapy with antibodies against PD-1/PD-L1 and CTLA-4 is that inhibition of the PD-1 and PD-L1 pathways cannot stimulate cancer immunity when target lymphocytes (CD8+ T cells) are absent from the tumor microenvironment. However, concurrent use of anti-CTLA-4 antibody ensures inhibition of the B7-CTLA-4 pathway, resulting in CD8+ T cell proliferation in the lymph nodes and their infiltration into tumor tissues, thus strengthening antitumor effects. In addition, anti-CTLA-4 antibody in the tumor microenvironment can inhibit the tumor suppressive effect of Tregs, which express surface CTLA-4. Based on this rationale, several studies are currently investigating the utility of combination therapy with antibodies against CTLA-4, PD-1, and PD-L1 in HCC (Table 2).

The efficacy of nivolumab and the anti-CTLA-4 antibody ipilimumab has been evaluated in the CheckMate 040 study using various doses and intervals. Another current clinical trial is comparing the effects of combina-

tion therapy with the anti-PD-1 antibody and the anti-CTLA-4 antibody tremelimumab and monotherapy with each antibody in patients with HCC. Treatment outcomes from phase I of this phase I/II trial were presented at the 2017 annual meeting of ASCO, showing objective response rates of 25% in all 40 patients and 40% in the 20 uninfected patients, findings considered quite encouraging (Table 3) [23]. The phase II study is scheduled to end in April 2018.

Immune Checkpoint Inhibitors in Combination with Existing Locoregional Therapy

Other studies are evaluating a different treatment approach for HCC by combining immune checkpoint inhibitors and conventional locoregional therapy. Radiotherapy and locoregional therapies, such as transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA), are thought to activate the immune system and improve the effect of immunotherapy by inducing local inflammation and the release of neoantigens. Accordingly, these locoregional therapies are particularly

Fig. 8. Phase II exploratory trial design of adjuvant treatment with anti-PD-1 antibodies in the prevention of recurrence after curative treatment of HCC, which is currently being conducted only in Japan. HCC, hepatocellular carcinoma; IC, informed consent.

Fig. 9. Phase Ib lenvatinib plus pembrolizumab in hepatocellular carcinoma, currently being conducted only in Japan. DLT, dose-limiting toxicity; BW, body weight; BCLC, Barcelona Clinic Liver Cancer; pts, patients; SAE, severe adverse effect.

useful for tumors that do not release enough TAA. A recent clinical study reported the treatment efficacy of anti-CTLA-4 antibody combined with locoregional therapy in patients with advanced HCC [24]. In this study (NCT# 01853618), the anti-CTLA-4 antibody tremelimumab was used as adjuvant therapy after performing TACE or RFA on some nodules in patients with advanced HCC. The rate of partial reduction was 26%, and median time to progression and overall survival were 7.4 and 12.3 months, respectively. Moreover, this combination therapy increased the number of CD3+ and CD8+ cells in un-

treated nodules induced by locoregional therapy, a rare phenomenon referred to as the abscopal effect.

These findings suggest that immune checkpoint inhibitors (anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies) can be used in combination with TACE or as adjuvant therapy after resection or RFA (Fig. 7).

Tumor recurrence rates are particularly high in patients with HCC, even after curative treatment such as resection or RFA. This is largely attributable to microsatellite lesions that were not detected by preoperative diagnostic imaging. Several clinical trials have evaluated the

Fig. 10. Mechanism of synergistic effect by a combination therapy of lenvatinib and PD-1 antibody. **a** Immunosuppressive microenvironment and PD-1/PD-L1 immunosuppression. **b** Lenvatinib and anti-PD-1/PD-L1 antibodies synergistically induce PD-1/PD-L1 blockade and inhibit the immunosuppressive microenvironment.

effects of adjuvant treatment with interferon, retinoids, vitamin K, or sorafenib in patients with these microsatellite lesions, but none has yielded positive outcomes [25–28].

TACE [29–32] and RFA [33–35] induce tumor immunogenicity by releasing TAA and stimulating the migration of cytotoxic T lymphocytes to small intrahepatic metastatic nodules. Thus, subsequent administration of an anti-PD-1 antibody may control these small intrahepatic metastatic nodules [36]. For example, RFA was found to significantly increase the number of tumor antigen-specific T cells in 62% of patients, confirming the release of TAA. This study also showed that recurrence-free survival rates were significantly higher among patients with high levels of tumor antigen-specific T cells than among those with low levels of tumor antigen-specific T cells [37].

An investigator-initiated clinical trial in Japan is ongoing evaluating the utility of nivolumab as adjuvant therapy after resection [38, 39] or ablation. The combined use of immune checkpoint inhibitors under adjuvant conditions after curative treatment with RFA is expected to serve as an appropriate treatment strategy for preventing recurrence of HCC (Fig. 8).

Concurrent Use of Immune Checkpoint Inhibitors and Molecularly Targeted Agents

Combination therapy with immune checkpoint inhibitors and molecularly targeted agents [40, 41] has received considerable attention in recent years. Factors that may contribute to the immunosuppressive hepatic environment in patients with liver cancer include hepatic interstitial cells, such as Kupffer cells, dendritic cells, endothelial cells, and hepatic stellate cells, and immunosuppressive cytokines, such as interleukin (IL)-10 and transforming growth factor (TGF)- β , as well as the PD-1/PD-L1 pathway. This immunosuppressive environment may be inhibited by combinations of molecularly targeted agents and immune checkpoint inhibitors [42, 43].

Table 4 shows ongoing clinical trials of combination treatments with immune checkpoint inhibitors and molecularly targeted agents. The efficacy of combination therapy with pembrolizumab and lenvatinib in HCC is being tested in Japan (Fig. 9). Previous studies of this combination, presented at ESMO 2016 and ASCO 2017, reported high response rates (50–70%) and long-lasting drug effects (durable response) in patients with solid cancer such as renal and endometrial cancers [44, 45].

Fig. 11. Improved overall survival as a result of combination therapy of molecular targeted therapy and immune checkpoint inhibitor will be realistic in the very near future. MST, median survival time; pts, patients. Adapted from Sharma and Allison [46].

Unlike concurrent administration of 2 immune checkpoint inhibitors (PD-1/PD-L1 antibody plus CTLA-4 antibody), combinations with molecularly targeted agents should result in cancer cell suppression by 2 different mechanisms of action. In a preclinical study, pembrolizumab and lenvatinib inhibited cancer immunosuppressive environments induced by tumor-associated macrophages and Tregs, reducing the levels of TGF- β and IL-10, the expression of PD-1, and the inhibition of Tim-3, and thereby triggering anticancer immunity mediated by immunostimulatory cytokines such as IL-12 [44] (Fig. 10). These studies may provide insight into the appropriate molecularly targeted agents to be used with immune checkpoint inhibitors.

Conclusion

Patients who respond favorably to combinations of molecularly targeted agents and immune checkpoint inhibitors may show prolonged survival or achieve a cure [46, 47] (Fig. 11). In addition to prolonging the survival of patients with HCC, combinations of immune checkpoint inhibitors with molecularly targeted agents or locoregional therapy may bring about a true cure, thus causing a paradigm shift in liver cancer therapy. Liver cancer represents a group of highly heterogeneous lesions with variable etiopathogenesis, including viral and non-viral hepatitis. Many patients with liver cancer have impaired liver function and poor physical performance, re-

quiring a variety of treatment options. The invention of immune checkpoint inhibition and the combination strategies centered on checkpoint inhibitors may drastically change the conventional treatment algorithms for HCC.

Disclosure Statement

The author has no conflicts of interest to declare.

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