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Editorial

Combination Cancer Immunotherapy in Hepatocellular Carcinoma

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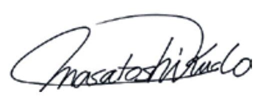

Editor *Liver Cancer*

Introduction

Combination cancer immunotherapy is becoming a major topic in cancer therapy research including in hepatocellular carcinoma (HCC). Well-known combinations include two types of immune checkpoint inhibitors (anti-PD-1/PD-L1 and anti-CTLA-4 antibodies), anti-PD-1/PD-L1 antibody with a molecular targeted agent, and anti-PD-1/PD-L1 or -CTLA-4 antibody with existing locoregional therapies (Fig. 1).

Immunotherapy for the treatment of various types of cancer has advanced rapidly in recent years. The Federal Drug Administration (FDA) designated nivolumab, an anti-PD-1 antibody, as a breakthrough therapy in 2014, and pembrolizumab, another anti-PD-1 antibody, also received this designation. Nivolumab was approved as a highly effective agent for the treatment of certain malignancies, including malignant melanoma, non-small cell lung cancer, kidney cancer, Hodgkin lymphoma, head and neck cancer, and gastric cancer [1–6]. Promising clinical trials evaluating this agent for the treatment of many other types of cancer are currently ongoing. HCC is more heterogeneous than other types of solid cancer and hematological malignancies, and is not associated with a specific driver mutation. HCC cannot be treated with agents that impair liver function, and thus requires different therapeutic strategies than those used for other cancers. Despite this limitation, the CheckMate 040 study revealed that nivolumab is a promising therapy for HCC [7]. Many pharmaceutical companies started phase III or earlier-phase trials of anti-PD-1/PD-L1 antibodies for HCC treatment (Table 1). In addition, the FDA approved nivolumab for second-line therapy after sorafenib in September 2017.

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Table 1. Immune checkpoint inhibitors in hepatocellular carcinoma 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	Tecentriq	Fully humanized IgG1 antibody	Roche
	PD-L1	MEDI4736	Durvalumab	Imfinzi	Humanized IgG1 antibody	AstraZeneca
	PD-L1	MSB-0010718C	Avelumab	Bavencio	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

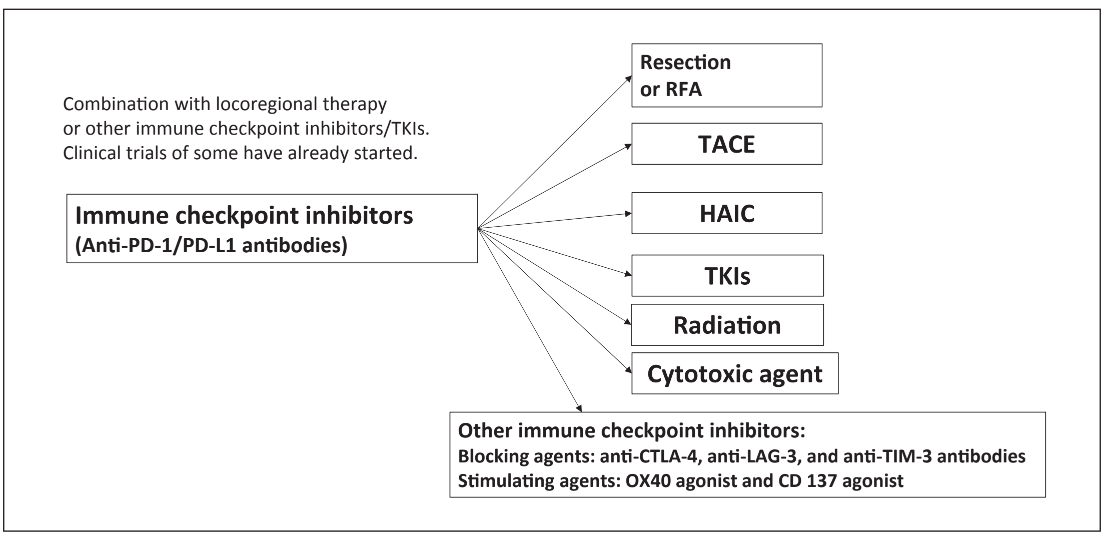

Fig. 1. Treatment strategy using immune checkpoint inhibitors. Future direction: combination therapy. RFA, radiofrequency ablation; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; TKIs, tyrosine kinase inhibitors.

Combination of Immune Checkpoint Inhibitors

Anti-PD-1/PD-L1 and anti-CTLA-4 antibodies are expected to be promising agents in HCC immunotherapy, and clinical trials evaluating the simultaneous blockade of multiple immune checkpoints are currently ongoing (Fig. 1; Table 2). The high efficacy of combination therapy was demonstrated in malignant melanoma [6], and a trial of the same combination for the treatment of HCC is currently ongoing [8]. Inhibition of the PD-1/PD-L1 pathway will not activate tumor immunity as expected if the required $CD8^+$ T cells are not present in the cancer tissue. However, simultaneous inhibition of the B7-CTLA-4 pathway by an anti-CTLA-4 antibody can increase the number of activated $CD8^+$ T cells in lymph nodes, followed by an

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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	1L/2L	Cohort 1: dose escalation	DLT/MTD	Completed
	CheckMate 040	NCT01658878	BMS/ONO	I/II	214	1L/2L	Cohort 2: dose expansion	ORR	Completed
	CheckMate 040	NCT01658878	BMS/ONO	I/II	200	1L	Cohort 3: nivolumab vs. sorafenib	ORR	Completed
	CheckMate 040	NCT01658878	BMS/ONO	I/II	120	2L	Cohort 4: nivolumab + ipilimumab	Safety/ tolerability	Completed
	CheckMate 040	NCT01658878	BMS/ONO	I/II	–	1L	Cohort 5: nivolumab (Child-Pugh B)	ORR	Completed
	CheckMate 040	NCT01658878	BMS/ONO	I/II	–	1L	Cohort 6: nivolumab + cabozantinib	ORR	Recruiting
	CheckMate 040	NCT01658878	BMS/ONO	I/II	–	1L	Cohort 7: nivolumab + ipilimumab + cabozantinib	ORR	Recruiting
	CheckMate 459	NCT02576509	ONO	III	726	1L	Nivolumab vs. sorafenib	TTP/OS	Completed
Pembrolizumab									
Pembrolizumab (PD-1 Ab)	KEYNOTE-224	NCT02702414	MSD	II	100	2L	Pembrolizumab (1 arm)	ORR	Completed
Pembrolizumab (PD-1 Ab)	KETNOTE-240	NCT02702401	MSD	III	408	2L	Pembrolizumab vs. placebo	PFS/OS	Recruiting
Durvalumab									
Durvalumab (PD-L1 Ab)/ tremelimumab (CTLA-4 Ab)	–	NCT02519348	AstraZeneca	II	144	1L/2L	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
Durvalumab ± tremelimuab vs. Sorafenib		NCT03298451	AstraZeneca	III	–	1L	Durvalumab ± tremelimuab vs. sorafenib	OS	Recruiting
MSBoo11359C (PD-L1 Ab + TGFB Trap)	–	NCT02699515	Merk Serono	I	–	1L	1 arm	Safety/ tolerability	Recruiting
PDR001 + INC280	–	NCT02795429	Novartis	I/II	–	1L/2L	PDR001 + INC280	Safety/ORR	Active accrual
LY3300054 + LY3321367	–	NCT03099109	Eli Lilly	I/II	–	1L/2L	LY3300054 + LY3321367	Safety/ORR	Active accrual

TACE, transarterial chemoembolization; RFA, radiofrequency ablation; DLT, dose-limiting toxicity; MTD, median survival time; ORR, overall response rate; TTP, time to progression; OS, overall survival.

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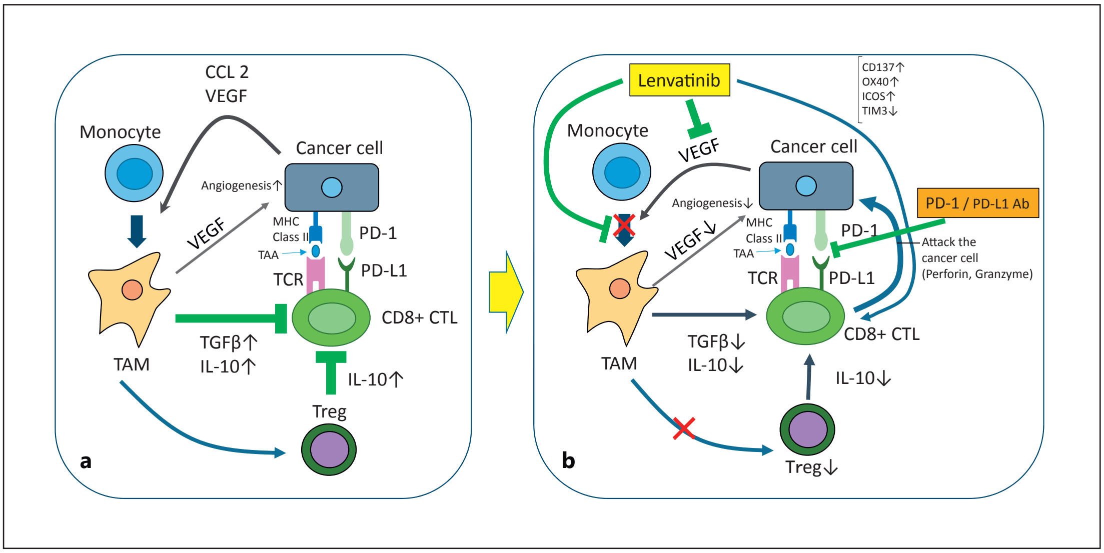

Fig. 2. Mechanism of synergistic effects of lenvatinib and anti-PD-1/PD-L1 antibodies. **a** Immunosuppressive microenvironment + PD-1/PD-L1 immunosuppression. **b** Lenvatinib + anti-PD-1/PD-L1 antibodies synergistically induce PD-1/PD-L1 blockade and inhibit the immunosuppressive microenvironment.

increase in the number of activated $CD8^+$ T cells infiltrating into tumor tissues, thereby enhancing the antitumor effects. In addition, anti-CTLA-4 antibody therapy may be effective against regulatory T cells in the cancer immunosuppressive microenvironment.

This is the rationale for the use of combination therapy with an anti-PD-1/PD-L1 antibody and an anti-CTLA-4 antibody, and several trials evaluating these combinations for the treatment of HCC are currently ongoing (Table 2). The CheckMate 040 study tested the efficacy of nivolumab in combination with ipilimumab at varying doses and dose intervals. Another trial comparing the efficacy and safety of combination therapy with durvalumab (anti-PD-L1 antibody) plus tremelimumab (anti-CTLA-4 antibody) to those of monotherapy is currently ongoing. The results of phase I of this phase I/II study were reported at the ASCO 2017 with favorable outcomes (ORR of 25.0% in 40 cases) [9]; the eagerly awaited phase II is expected to be completed in April 2018.

Combination of Immune Checkpoint Inhibitors and Molecular Targeted Therapy

The therapeutic outcomes of nivolumab plus ipilimumab are superior to those of monotherapy in melanoma [6, 10]. Therapy involving an immune checkpoint inhibitor plus a molecular targeted agent was suggested as a promising strategy in recent years. In HCC, interstitial cells (Kupffer cells, dendritic cells, liver endothelial cells, and liver stellate cells) and immunosuppressive cytokines (e.g., IL-10 or TGF-β) may contribute to the immunosuppressive environment, and the PD-1/PD-L1 pathway plays an important role in the development of the immunosuppressive microenvironment in HCC. Combining a molecular targeted agent and an immune checkpoint inhibitor is expected to improve this immunosuppressive microenvironment [11] (Fig. 2).

Table 3 shows the currently ongoing trials evaluating combination therapy involving immune checkpoint inhibition with molecular targeted therapy. A trial evaluating the combination of pembrolizumab and lenvatinib for the treatment of HCC was started in Japan and

Table 3. Immune checkpoint inhibitors in combination with tyrosine kinase inhibitors in hepatocellular carcinoma

Phase	Target	Agent	Company	Trial #
1–2	PD-1 + TGF-β receptor I	Nivolumab + galunisertib (LY2157299)	Eli Lilly	NCT02423343
1	PD-L1 + VEGFR-2	Ramucirumab + durvalumab (MEDI4736)	Eli Lilly	NCT02572687
1	PD-1 + multikinase	Pembrolizumab + lenvatinib	Eisai	NCT03006926
1	PD-1 + multikinase	Pembrolizumab + nintedanib	Gustave Roussy	NCT02856425
1	PD-1 + multikinase	PDR001 + sorafenib	Novartis	NCT02988440
1–2	PD-1 + c-Met	PDR001 + capmatinib (INC280)	Novartis	NCT02795429
1–2	PD-1 + CTLA-4 + MET/VEGFR2	Nivolumab + ipilimumab + cabozantinib	BMS	NCT01658878
1	PD-1 + multikinase	Nivolumab + lenvatinib	Ono	
1–2	PD-L1 + multikinase	Avelumab + axitinib	Pfizer	NCT03289533
1–2	PD-L1 + multikinase	Atezolizumab + bevacizumab	Roche	

then will be expanded to the rest of the world. High response rates (50–70%) and the long-lasting durable response of this combination therapy in other types of solid cancer (e.g., kidney cancer and endometrial cancer) were presented at the ESMO 2016 and ASCO 2017. Therefore, similar high response rates and long-lasting durable responses are highly expected in HCC as well.

The mechanism underlying the synergistic effect of an immune checkpoint inhibitor plus a molecular targeted agent, unlike that of the combination of two immune checkpoint inhibitors, needs to be thoroughly clarified. Regarding the mechanism of action of pembrolizumab-lenvatinib combination therapy [12], a preclinical study including in vitro and in vivo studies showed that suppression of tumor-associated macrophages, regulatory T cells, and other constituents of the tumor-suppressive microenvironment resulted in decreases in TGF-β and IL-10, the downregulation of PD-1 and Tim3, and the upregulation of ICOS and OX40, thereby inducing tumor immunity through IL-12 [13] (Fig. 2). It is anticipated that similar future studies on HCC will identify the best combination between a specific immune checkpoint inhibitor and molecular targeted agent. In addition to pembrolizumab-lenvatinib combination therapy (Fig. 3), many similar combination therapies for HCC are currently being evaluated in early-phase clinical trials (Table 3).

Combination of Immune Checkpoint Inhibitors with an Existing Locoregional Therapy

A different approach, namely, combining an immune checkpoint inhibitor with an existing locoregional therapy for HCC, is currently under evaluation. Transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA), or radiation therapy is expected to enhance the effects of immunotherapy by inducing local inflammation. This would lead to the release of neoantigens that activate antigen presentation and the relevant immune system activation. These locoregional therapies are particularly beneficial when the levels of cancer antigens are negligible because of poor antigen release. The results of combination therapy with an anti-CTLA-4 antibody and locoregional therapy in advanced HCC were recently published [14]. The NCT01853618 study evaluated the efficacy of adjuvant therapy with tremelimumab (anti-CTLA-4 antibody) after RFA or TACE in several, but not all, HCC nodules, with favorable outcomes, including a partial response rate of 26%, time to tumor progression of 7.4 months, and overall survival of 12.3 months. Increases in $CD3^+$ and $CD8^+$ cells in untreated nodules were clearly confirmed and attributed to the abscopal effect.

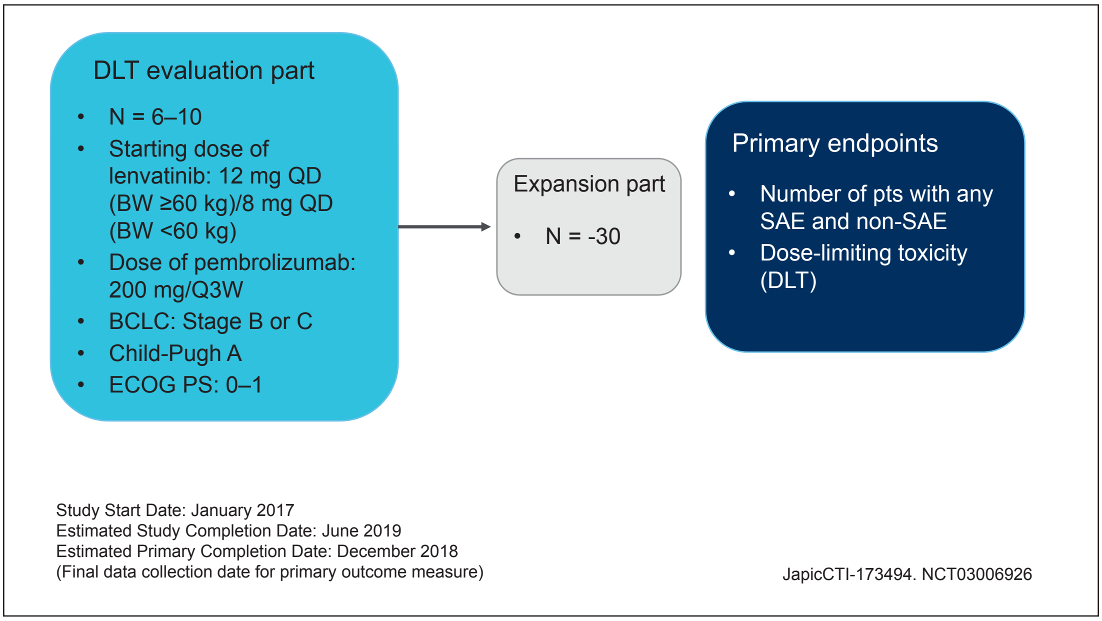

Fig. 3. Phase Ib study of lenvatinib plus pembrolizumab in hepatocellular carcinoma.

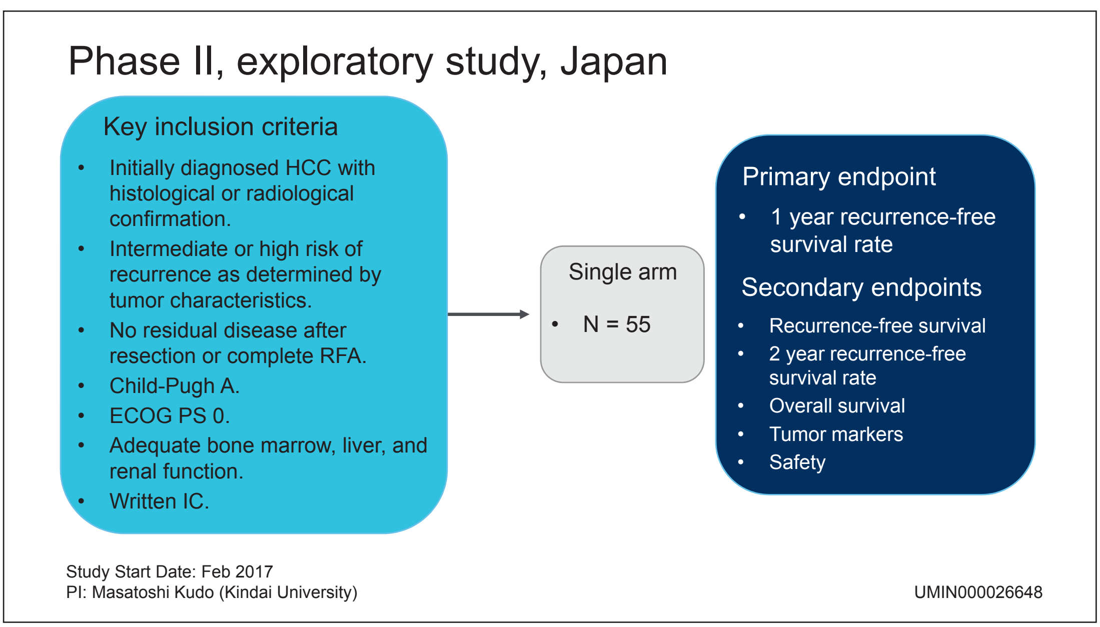

Fig. 4. Adjuvant treatment with anti-PD-1 antibody to prevent recurrence after curative treatment of HCC. HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IC, informed consent.

Immune checkpoint inhibitors (antibodies to PD-1, PD-L1, and CTLA-4) are potentially beneficial in all forms of neoadjuvant therapy, adjuvant therapy after resection or ablation, and in combination with TACE, cytotoxic chemotherapy, or radiotherapy (Fig. 1).

HCC recurrence rates after curative therapy (resection or ablation) are particularly high, and its management remains an unmet need. This is mainly because of the presence of

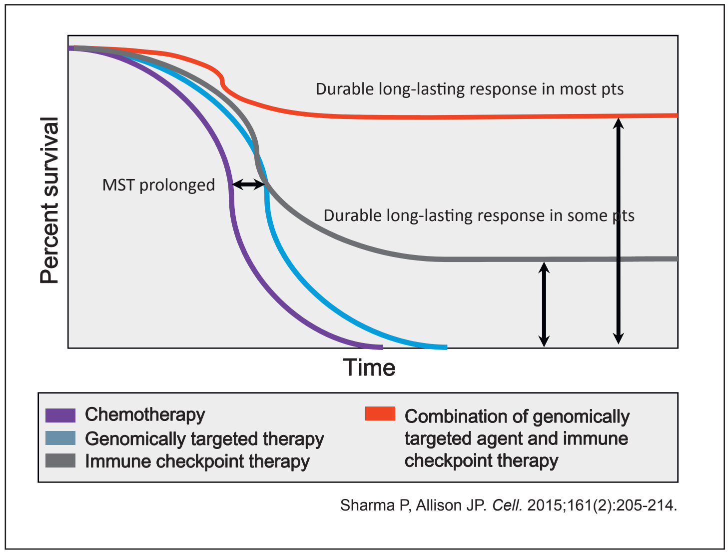

Fig. 5. Improved overall survival as a result of combination therapy: very near future. MST, median survival time.

extremely small microsatellite metastatic lesions that are undetectable by imaging even at the time of resection or ablation. To address this issue, various agents (e.g., IFN, peretinoin, vitamin K, and sorafenib) were tested for their efficacy as an adjuvant therapy in clinical trials, although all showed negative results [15–18].

Theoretically, microsatellite lesions and intrahepatic metastases may be suppressed by administration of anti-PD-1 antibody after recruitment of cytotoxic T lymphocytes to the microsatellite lesions upon release of tumor antigens by TACE or RFA [19]. Mizukoshi et al. [20] observed a significant increase in tumor-specific T cells, which is indicative of post-treatment tumor antigen release, after RFA in 62% of patients, and a significant correlation between tumor-specific T cells and recurrence-free survival.

A clinical trial of nivolumab in the adjuvant setting after curative treatment was started in February 2017 in Japan (Fig. 4). The combination strategy of an immune checkpoint inhibitor in the adjuvant setting with curative therapy (resection or RFA) is anticipated to prevent HCC recurrence effectively.

Conclusion

Padmanee Sharma and James P. Allison predicted the possibility of long-term survival and real cure in patients who responded to combination treatment with immune checkpoint inhibitors and molecular targeted agents because its high efficacy can lead to “cure in a real sense” [21, 22] (Fig. 5). Indeed, immune checkpoint inhibitors will extend the overall survival of HCC patients, and, further, combination therapy with molecular targeted agents may result in real cure, which might lead to a paradigm shift in the treatment of HCC.

Emerging therapeutic strategies involving immune checkpoint inhibition combined with other treatment modalities will definitely change the future landscape of HCC treatment.

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