Immune Checkpoint Blockade in Hepatocellular Carcinoma: 2017 Update

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Editor *Liver Cancer*

Introduction

The immune checkpoint molecule programmed cell death 1 (PD-1) was discovered in 1992 by Professor Tasuku Honjo and his research team at Kyoto University [1]. They later discovered that PD-1 is involved in immunosuppression and is a receptor that acts as a “brake” for the immune response in knockout mice. In 2000, a joint research project between the Honjo group at Kyoto University and the Genetics Institute together with Harvard University discovered the ligands of PD-1 (PD-L1 and PD-L2) [2–5]. In 2002, Iwai et al. [6] found that enhancing immune activation by inhibiting the binding of PD-1 to its ligands in mouse models markedly enhanced antitumor activity. In 2005, Ono Pharmaceutical and the American company Medarex took note of these findings and developed nivolumab, a human anti-PD-1 antibody. That same year, the U.S. Food and Drug Administration (FDA) recognized nivolumab as an investigational new drug, thereby enabling clinical trials to be started in the United States. In 2009, Bristol-Myers Squibb and Ono Pharmaceutical (BMS/ONO) began joint clinical trials of nivolumab. The results of clinical trials in patients with melanoma led to the approval of an anti-PD-1 antibody for the treatment of melanoma in Japan in July 2014, before any other country in the world. Nivolumab has also been evaluated in a series of clinical trials for non-small cell lung cancer and renal cell carcinoma and has yielded favorable outcomes.

In 1995, Dr. James Allison of the University of Texas discovered that another molecule, called cytotoxic T-lymphocyte-associated antigen (CTLA-4) [7], serves as an indicator of immune cell suppression [7]. In 1996, his team showed that tumors disappeared in mice treated with an antibody that inhibits the function of CTLA-4 [8]. CTLA-4 is also an immune checkpoint molecule. Bristol-Myers developed an anti-CTLA-4 antibody called ipilimumab, which was approved for the treatment of melanoma in the United States in March 2011 and in Europe in July 2011 [9]. It was later approved in Japan in July 2015.

When cancer cells develop, antigen-presenting cells (APCs) recognize tumor-associated antigens (TAAs), triggering in the lymph nodes the activation of immature T cells that will become CD8-positive T cells (the priming phase). Once activated, the T cells travel throughout the bloodstream and reach the tumor site. There, they attempt to attack tumor cells by

Fig. 1. The cancer–immunity cycle. The generation of immunity to cancer is a cyclic process that leads to an accumulation of immune-stimulatory factors. This cycle can be divided into seven major steps, starting with the release of antigens from cancer cells and ending with the killing of cancer cells. CTLs=cytotoxic T lymphocytes. Reproduced with permission from Chen DS, et al. [10]

releasing molecules such as perforin and granzymes (the effector phase) (fig 1) [10]. Moreover, recognition of TAAs by T cell receptors (TCR) triggers the release of interferon gamma (IFN- γ) and other cytokines by CD8-positive T cells in an attempt to attack the cancer. However, tumor cells protect themselves by expressing IFN- γ induced PD-L1 or PD-L2, which binds to PD-1. When this happens, PD-1/PD-L1 binding attenuate the antitumor immune response, thereby weakening the attacking power of the T cells. This is called immune escape or immune tolerance (fig. 2). The anti-PD-1 antibody blocks PD-1 on activated T cells from binding to PD-L1 or PD-L2 on APCs or tumor cells. This removes the “brake” on the immune system and restores the ability of T cells to attack tumor cells (fig. 3). Unlike conventional chemotherapy or molecular targeted therapy, anti-PD-1 antibody achieves its antitumor effect by restoring the original potential of the natural human immune system as a powerful and precise weapon against cancer cells [11–22]. Antibodies against PD-L1 expression in the cancer tissue are believed to have a similar effect [23]. The recognition of “immuno-oncology” using immune checkpoint inhibitors was considered the “Breakthrough of the Year” by the American journal *Science* in 2013, and immuno-oncology has been widely publicized. PD-L1 also serves as a biomarker that predicts the response to anti-PD-1 antibody [24]. In addition, Kupffer-phase Sonazoid contrast-enhanced ultrasonography is an effective imaging method for predicting the response to treatment with anti-PD-1 antibody [25].

Development of Immune Checkpoint Inhibitors for Hepatocellular Carcinoma (HCC)

Promising results from an interim analysis of a phase I/II trial of the anti-PD-1 antibody nivolumab (CheckMate-040 trial dose-escalation cohort) were presented at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting held in Chicago [26, 27]. This

Fig. 2. Immune checkpoint molecule: PD-1, PD-L1, CTLA-4. Immune checkpoint molecules such as PD-1, PD-L1, and CTLA-4 play an important role in the immune escape of cancer cells from activated CD8-positive T cells. MHC=major histocompatibility complex; IFN γ R=interferon gamma receptor.

dose-escalation study demonstrated the safety of nivolumab at doses of 3 mg/kg and 10 mg/kg in HCC patients with hepatitis C virus (HCV) infection, patients with hepatitis B virus (HBV) infection, and uninfected patients. The interim results of the dose-escalation study also demonstrated the efficacy of nivolumab at doses ranging from 0.1 to 10 mg/kg. Of the 47 patients included in the study, 33 (70%) had extrahepatic metastasis, 6 (13%) had vascular invasion, and 32 (68%) had previously been treated with sorafenib, i.e., the study population had relatively advanced cancer. Patients were treated with anti-PD-1 antibody, and an interim analysis was performed on March 12, 2015. At that point, 17 patients were still receiving treatment and 30 had completed or discontinued treatment. The reasons for discontinuation were disease progression in 26 patients, complete response (CR) in two patients, and adverse events in two patients. The adverse events leading to discontinuation were increased bilirubin (n=1) and an event unrelated to the study drug (n=1). The only grade 4 event (graded using the Common Terminology Criteria for Adverse Events) was increased lipase, and the only grade 3 events were elevated aspartate aminotransferase (AST) levels in five patients (11%) and elevated alanine aminotransferase (ALT) levels in four patients (9%). No serious liver dysfunction or autoimmune disease was reported.

The response rate was 19% (n=8), including the two CRs (5%). The disease control rate (DCR) was also very favorable: 67% of patients (n=28) maintained stable disease (SD) or better, whereas only 33% (n=14) developed progressive disease (PD).

Waterfall plots showed that the tumor size decreased to some extent in all cohorts (i.e., uninfected, HBV-infected, and HCV-infected HCC patients). The durability of treatment responses is particularly noteworthy. The two patients who had a CR achieved it within 3 months and maintained it for 18 months. Another patient who showed a partial response (PR) (almost a CR in fact) showed SD at approximately 11 months while the PR occurred at approximately 13 months. A durable response was achieved in all patients with a PR or SD, and no patient developed PD because of resistance. In summary, treatment of liver cancer with anti-PD-1 antibody yielded a durable response comparable to that achieved in other types of cancer. This property is highly characteristic of immune checkpoint inhibitors and merits attention. The two patients who had a CR achieved it within 3 months and maintained the response for 18 months or longer, even after discontinuing the anti-PD-1 antibody a few months after the

Fig. 3. Immune checkpoint blockade: anti-PD-1, anti-PD-L1, and anti CTLA-4 antibody. Anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies restore cytotoxic T cell activity, resulting in tumor attack by perforin and granzyme.

CR. Almost all patients who showed a PR achieved it within 3 months of treatment. One of the cases presented at ASCO 2015 was a patient with countless bilobar HCCs, all of which resolved completely after 6 weeks; this was accompanied by a decrease in alpha-fetoprotein from 21,000 to 283 ng/ml. Another patient showed a decrease in tumor size from 10 cm to about 2 cm after 48 weeks, which demonstrates the durability of the response. The overall 12-month survival rate was a favorable 62%, which is a very promising outcome considering the unfavorable tumor characteristics of the study population.

The interim results of this trial can be summarized in three points: First, monotherapy with the anti-PD-1 antibody nivolumab has a favorable safety profile for HCC that is comparable with its safety profile for the treatment of other types of cancer. Second, nivolumab can be used safely in patients infected with HBV or HCV. Third, immunotherapy yields both a very high response rate and a durable response. This long-lasting effect was observed at all dose levels and in all cohorts (uninfected, HBV-infected, and HCV-infected).

The team conducting this phase I/II trial designed an expansion study using a fixed dose of 3 mg/kg of nivolumab in three cohorts as follows: patients with no HBV or HCV infection who were sorafenib-naïve (n=50) or who had developed PD after treatment with sorafenib (n=50); HCV-infected patients (n=50); and HBV-infected patients (n=50). The results of the expansion study and the final results from the dose-escalation study were presented at ASCO 2016.

Clinical Trials in Progress

According to the results presented at ASCO 2016, 35 of the 214 patients (16%) in the expansion cohort (CheckMate-040 cohort 2) had a tumor response [28] (table 1). The response rate was 20% for uninfected sorafenib-naïve or sorafenib-intolerant HCC patients, 19% for uninfected sorafenib-treated patients with PD, 14% for HCV-infected patients, and 12% for HBV-infected patients. The 9-month survival rate was a favorable 70.8%. Grade 3-4 adverse events of elevated AST and ALT levels were observed in this expansion cohort at low

Table 1. CheckMate 040 dose-expansion cohort (n=214) investigator-assessed best overall response (RECIST v1.1)

	Uninfected: sorafenib naïve/ intolerant (n=54)	Uninfected: sorafenib progressors (n=58)	HCV (n=51)	HBV (n=51)	Total (n=214)
Objective response, n (%)	11 (20)	11 (19)	7 (14)	6 (12)	35 (16)
CR	0	2 (3)	0	0	2 (1)
PR	11 (20)	9 (16)	7 (14)	6 (12)	33 (15)
SD	32 (59)	27 (47)	29 (57)	23 (45)	111 (52)
PD	11 (20)	18 (31)	12 (24)	22 (43)	63 (29)
Not evaluable	0	2 (3)	3 (6)	0	5 (2)

RECIST=response evaluation criteria in solid tumors. Reproduced with permission from Sangro B, et al. [28]

Table 2. CheckMate 040 dose-expansion cohort (n=214) treatment-related adverse events (TRAEs)

	Uninfected (n=112)		HCV (n=51)		HBV (n=51)		Total (n=214)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Patients with any TRAE, n (%)	72 (64)	21 (19)	37 (73)	15 (29)	30 (59)	3 (6)	139 (65)	39 (18)
Symptomatic TRAEs reported in >4% of all patients								
Fatigue	31 (28)	2 (2)	7 (14)	0	7 (14)	0	45 (21)	2 (1)
Pruritus	11 (10)	0	11 (22)	0	11 (22)	0	33 (15)	0
Rash	12 (11)	1 (1)	8 (16)	0	6 (12)	0	26 (12)	1 (0.5)
Diarrhea	16 (14)	2 (2)	3 (6)	0	1 (2)	1 (2)	20 (9)	3 (1)
Nausea	8 (7)	0	6 (12)	0	0	0	14 (7)	0
Decreased appetite	5 (5)	0	2 (4)	0	3 (6)	0	10 (5)	0
Dry mouth	5 (4)	0	1 (2)	0	2 (4)	0	8 (4)	0
Laboratory-value TRAEs reported in >4% of all patients								
ALT increased	6 (5)	2 (2)	7 (14)	4 (8)	2 (4)	0	15 (7)	6 (3)
AST increased	7 (6)	3 (3)	6 (12)	6 (12)	0	0	13 (6)	9 (4)
Platelet count decreased	4 (4)	1 (1)	3 (6)	2 (4)	5 (10)	1 (2)	8 (4)	3 (1)
Anemia	2 (2)	0	3 (6)	1 (2)	3 (6)	0	8 (4)	1 (0.5)

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rates of 6% (13/139) and 7% (15/139), respectively (table 2). Considering that 66% of the 214 patients had been previously treated with sorafenib, and a high percentage of patients had advanced cancer, a 9-month survival rate of 70.8% is an excellent result (tables 3, 4).

The results of additional analysis of the dose-escalation cohort of 48 patients (CheckMate-040 cohort 1) showed a tumor response in seven patients (15%); the response rate was 13% in the uninfected group, 30% in the HCV-infected group, and 7% in the HBV-infected group [29] (tables 5–7).

The team conducting this phase I/II trial in addition to cohort 1 and 2, a randomized controlled study comparing nivolumab with sorafenib (cohort 3), a study of combination therapy

Table 3. CheckMate 040 dose-expansion cohort (n=214) baseline patient characteristics and prior treatment history

	Uninfected: sorafenib naïve/ intolerant (n=54)	Uninfected: sorafenib progressors (n=58)	HCV (n=51)	HBV (n=51)	Total (n=214)
Median age (range), years	66 (20–83)	65 (19–80)	65 (53–81)	55 (22–81)	64 (19–83)
Male, n (%)	46 (85)	43 (74)	43 (84)	39 (77)	171 (80)
Ethnicity, n (%)					
White	36 (67)	35 (60)	30 (59)	4 (8)	105 (49)
Black/African American	1 (2)	1 (2)	2 (4)	2 (4)	6 (3)
Asian	16 (30)	22 (38)	18 (35)	45 (88)	101 (47)
Other	1 (2)	0	1 (2)	0	2 (1)
Extrahepatic metastases, n (%)	42 (78)	43 (74)	30 (59)	46 (90)	161 (75)
Vascular invasion, n (%)	1 (2)	3 (5)	5 (10)	6 (12)	15 (7)
Child–Pugh score, n (%)					
5	41 (76)	38 (66)	27 (53)	44 (86)	150 (70)
6	12 (22)	20 (34)	21 (41)	7 (14)	60 (28)
7	1 (2)	0	2 (4)	0	3 (1)
9	0	0	1 (2)	0	1 (0.5)
α-Fetoprotein >200 µg/L, n (%)	15 (28)	26 (45)	18 (35)	27 (53)	86 (40)
Prior treatment type, n (%)					
Surgical resection	29 (54)	37 (64)	19 (37)	40 (78)	125 (58)
Radiotherapy	7 (13)	17 (29)	5 (10)	12 (24)	41 (19)
Local treatment for HCC	25 (46)	33 (57)	29 (57)	40 (78)	127 (59)
Systemic therapy	22 (41)	57 (98)	32 (63)	46 (90)	157 (73)
Sorafenib	15 (28)	56 (97)	30 (59)	40 (78)	141 (66)

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Table 4. CheckMate 040 dose-expansion cohort (n=214) overall survival rates

Survival rate, %(95% CI) ^a	Uninfected: sorafenib naïve/ intolerant (n=54)	Uninfected: sorafenib progressors (n=58)	HCV (n=51)	HBV (n=51)	Total (n=214)
6-Month	89.8 (77.1, 95.6)	75.6 (61.5, 85.2)	82.1 (61.3, 92.4)	83.3 (67.6, 91.8)	82.5 (75.8, 87.5)
9-Month	79.8 (50.6, 92.8)	NC	NC	NC	70.8 (56.6, 81.1)

^aEstimated using the Kaplan–Meier method. CI=confidence interval; NC=not calculated. Reproduced with permission from Sangro B, et al. [28]

with the anti-CTLA-4 antibody ipilimumab (cohort 4), and a study of nivolumab in Child–Pugh B patients (cohort 5).

Other ongoing trials include the dose-expansion study (cohort 2), a phase III trial comparing first-line nivolumab (anti-PD-L1 antibody) with sorafenib, a phase III trial of pembrolizumab as second-line therapy after sorafenib failure, and a phase II trial of combination therapy with the anti-PD-L1 antibody durvalumab and the anti-CTLA-4 antibody tremelimumab (table 8). The results of a clinical trial of an anti-CTLA-4 antibody for the treatment of HCC were published in the *Journal of Hepatology* in 2013. However, the anti-CTLA-4 antibody

Table 5. CheckMate 040 dose-escalation cohort (n=48) baseline patient characteristics and prior treatment history

	Uninfected (n=23)	HCV (n=10)	HBV (n=15)	Total (n=48)
Median age (range), years	61 (22–79)	67 (55–83)	62 (41–75)	62 (22–83)
≥65 years, n (%)	8 (35)	6 (60)	6 (40)	20 (42)
Male, n (%)	17 (74)	6 (60)	13 (87)	36 (75)
Ethnicity, n (%)				
White	19 (83)	8 (80)	1 (7)	28 (58)
Asian	2 (9)	2 (17)	14 (88)	18 (38)
Black	2 (9)	0	0	2 (4)
Extrahepatic metastases, n (%)	18 (78)	6 (60)	13 (87)	37 (77)
Vascular invasion, n (%)	3 (13)	1 (10)	2 (13)	6 (13)
Child–Pugh score, n (%)				
5	19 (83)	8 (80)	14 (93)	41 (85)
6	4 (17)	2 (20)	1 (7)	7 (15)
α-Fetoprotein >200 µg/L, n (%) ^a	8 (35)	3 (30)	8 (53)	19 (40)
Prior treatment type, n (%)				
Surgical resection	15 (65)	8 (80)	13 (87)	36 (75)
Radiotherapy ^b (external or internal)	6 (26)	2 (20)	2 (13)	10 (21)
Local treatment for HCC ^c	11 (48)	8 (80)	12 (80)	31 (65)
Systemic therapy	18 (78)	6 (60)	15 (100)	39 (81)
Sorafenib	16 (70)	5 (50)	14 (93)	35 (73)

^aBaseline α-fetoprotein values were missing for one uninfected patient; ^bCould include radioembolization; ^cTACE, RFA, or percutaneous ethanol injection. Reproduced with permission from El-Khoueiry AB, et al. [29]

Table 6. CheckMate 040 dose-escalation cohort (n=48) TRAE

	Total (n=48)	
	Any grade	Grade 3-4
Patients with any TRAE, n (%)	38 (79)	12 (25)
Symptomatic TRAEs reported in >5% of all patients, n (%)		
Rash	11 (23)	0
Pruritus	7 (15)	0
Diarrhea	4 (8)	0
Asthenia	3 (6)	0
Decreased appetite	3 (6)	0
Dry mouth	3 (6)	0
Fatigue	3 (6)	1 (2)
Laboratory-value TRAEs reported in >5% of all patients, n (%)		
AST increased	10 (21)	5 (10)
Lipase increased	10 (21)	6 (13)
Amylase increased	9 (19)	1 (2)
ALT increased	7 (15)	3 (6)
Anemia	3 (6)	1 (2)
Hypoalbuminemia	3 (6)	0
Hyponatremia	3 (6)	0

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Table 7. CheckMate 040 dose-escalation cohort (n=48) investigator-assessed best overall response (RECIST v1.1)

	Uninfected (n=23)	HCV (n=10)	HBV (n=15)	Total (n=48)
Objective response, n (%)	3 (13)	3 (30)	1 (7)	7 (15)
CR	2 (9)	1 (10)	0	3 (6)
PR	1 (4)	2 (20)	1 (7)	4 (8)
SD	13 (57)	5 (50)	6 (40)	24 (50)
PD	6 (26)	2 (20)	7 (47)	15 (31)
Not evaluable	1 (4)	0	1 (7)	2 (4)
Ongoing response, n (%)	1 (33)	0	0	1 (14)

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was associated with a slightly higher rate of adverse events than the anti-PD-1 antibody [30] (table 9).

Future Perspectives

The previously described interim analysis results from the phase I/II trial for HCC (dose-expansion cohort) that were presented at ASCO 2016 involved monotherapy with anti-PD-1 antibody. The anti-PD-1 antibody nivolumab has been approved for certain malignancies, including melanoma, non-small-cell lung cancer, and kidney cancer, and is expected to yield favorable outcomes in ongoing trials for many other types of cancer [31–36]. HCC requires different treatment strategies compared with other solid tumors or hematologic malignancies because it is extremely heterogeneous, does not have any major driver mutations, and cannot be treated with drugs that reduce hepatic functional reserve. The outcomes of this phase I/II dose-expansion trial indicate that the anti-PD-1 antibody is a promising treatment for HCC.

Additionally, as mentioned in the previous section, many pharmaceutical companies have started phase III trials and other early phase clinical trials of anti-PD-1/PD-L1 antibody for the treatment of HCC, the results of which are eagerly awaited.

There are unmet needs in HCC management in various settings, including neoadjuvant or adjuvant therapy with resection or ablation, combination of anti-PD-1 antibody with transcatheter arterial chemoembolization (TACE) [37, 38], and first- and second-line treatment. The immune checkpoint-inhibiting anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies may prove useful for adjuvant therapy or combination therapy in all these settings. Immune checkpoint inhibitors could be particularly effective for the treatment of inflammation induced by TACE or radiofrequency ablation (RFA) [39, 40], which releases highly antigenic neoantigens into the bloodstream. A clinical trial of adjuvant therapy with anti-CTLA-4 antibody after TACE and RFA is currently underway (table 9). The results of the interim analysis for that trial were presented at ASCO 2016. Adjuvant therapy with anti-CTLA-4 antibody after non-curative RFA or TACE caused an increase in CD3-positive and CD8-positive cells, even for untreated nodules [41].

A most promising topic in this area is the combination of these antibodies (anti-PD-1/PD-L1 antibodies) with other drugs. Potential drug combinations include anti-CTLA4 antibodies (ipilimumab and tremelimumab) and molecular targeted drugs (sorafenib and oth-

Table 8. Current trials of immune checkpoint inhibitors

Drug	Trial name	Clinicaltrials.gov	Company	Phase	n	Line of therapy	Design	Endpoint	Status
Nivolumab									
Nivolumab (PD-1 Ab)	CheckMate 040	NCT01658878	BMS/ONO	I/II	42	1/2I	Cohort 1: Dose escalation	DLT/MTD	Completed
/ipilimumab (PD-L1 Ab)	CheckMate 040	NCT01658878	BMS/ONO	I/II	214	1/2I	Cohort 2: Dose expansion	ORR	Completed
	CheckMate 040	NCT01658878	BMS/ONO	I/II	200	1I	Cohort 3: Nivolumab vs sorafenib	ORR	Completed
	CheckMate 040	NCT01658878	BMS/ONO	I/II	120	2I	Cohort 4: Nivolumab + ipilimumab	Safety/tolerability	Completed
Nivolumab (PD-1 Ab)	CheckMate 459	NCT02576509	ONO	III	726	1I	Nivolumab vs sorafenib	TTP/OS	Recruiting
Pembrolizumab									
Pembrolizumab (PD-1 Ab)	KEYNOTE-224	NCT02702414	MSD	II	100	2I	Pembrolizumab (1 arm)	ORR	Completed
Pembrolizumab (PD-1 Ab)	KEYNOTE-240	NCT02702401	MSD	III	408	2I	Pembrolizumab vs placebo	PFS/OS	Recruiting
Durvalumab									
Durvalumab (PD-L1 Ab)	-	NCT02519348	AstraZeneca	II	144	1/2I	Durvalumab (Arm A) Tremelimumab (Arm B) Durvalumab + tremelimumab (Arm C)	Safety/tolerability	Recruiting

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

Table 9. Clinical trials of CTLA-4 antibody for the treatment of HCC

NCT no.	Agent	Design	Status	n	Stage	Results
01008358	Tremelimumab	II	Complete	20	III/IV	PR=17.6%, DCR=76% TTP=6.5 months HCV virologic response Grade 3 AST/ALT=45%
01853618	Tremelimumab + TACE/RFA/ cryoablation	I	Ongoing	29 14 TACE 10 RFA 5 Cryoablation	III/IV	Safe, feasible Immune cell infiltration (+) TTP=5.7 month Reduction in HCV viral load

ers). The combination of nivolumab and ipilimumab has yielded treatment outcomes superior to those of monotherapy with either drug in melanoma [31, 42].

Rapid advances in the field of immunotherapy have been made in other types of cancer. The FDA designated nivolumab as a breakthrough therapy in September 2014, and later did the same for pembrolizumab. This raised hopes that anti-PD-1 and anti-PD-L1 antibodies will be approved for the treatment of HCC in the near future. The outcomes of liver cancer treatment strategies are widely expected to improve through the application of multidrug and locoregional therapies centered on immune checkpoint inhibitors. The field is in the middle of a paradigm shift in not only systemic therapy, but also comprehensive treatment strategies, including locoregional therapy for liver cancer.

Conclusion

Having advanced through the first stage of chemotherapy centered on cytotoxic agents and the second stage of chemotherapy centered on molecular targeted therapies, we are now poised to enter a third stage of cancer treatment strategies centered on immune checkpoint inhibitors. These strategies promise to become an essential element in cancer treatment, and advances in this area will bring the paradigm shift in cancer treatment.

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