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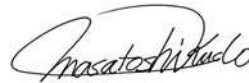**Editorial**

Molecular Targeted Agents for Hepatocellular Carcinoma: Current Status and Future Perspectives

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Editor *Liver Cancer*

Introduction

Locoregional therapy is the primary treatment for hepatocellular carcinoma (HCC). Sorafenib was approved as a first-line systemic therapy for advanced HCC with associated extrahepatic spread and/or vascular invasion in 2007. However, there are several limitations associated with sorafenib therapy. To overcome these problems, various clinical trials have been conducted to develop additional molecular targeted agents for HCC. However, all of the clinical trials conducted thus far, except for a recent trial using regorafenib, have been unsuccessful, emphasizing the difficulties associated with drug development for HCC. In this editorial, we review the current status and future prospects of molecular targeted agents that are being developed for HCC.

Sorafenib

The multikinase inhibitor sorafenib was the first oral molecular targeted agent to show a survival benefit in patients with HCC [1, 2]. In Japan, sorafenib was approved for national health insurance coverage in May 2009, and it has since been administered to more than 26,000 patients.

Liver Cancer

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102

Kudo: Molecular Targeted Agents for Hepatocellular Carcinoma: Current Status and
Future Perspectives

Table 1. Phase III clinical trials for HCC

Target population		Design	Trial name	Presentation	Publication
Early	Adjuvant (prevention of recurrence)	1. Peretinoin vs. placebo[a] 2. Sorafenib vs. placebo[a] 3. Peretinoin vs. placebo	NIK-333 STORM NIK-333/K-333	ASCO 2010 ASCO 2014 Ongoing	JG 2014 Lancet-O 2015
Intermediate	Improvement of TACE	1. TACE +/– sorafenib[a] 2. TACE +/– brivanib[a] 3. TACE +/– orantinib[a]	Post-TACE BRISK-TA ORIENTAL	ASCO-GI 2010 ILCA 2013 EASL 2015	EJC 2011 Hepatol 2014
Advanced	First line	1. Sorafenib vs. sunitinib[a] 2. Sorafenib vs. brivanib[a] 3. Sorafenib vs. linifanib[a] 4. Sorafenib +/– HAIC[a] 5. Sorafenib vs. lenvatinib 6. Sorafenib vs. nivolumab	SUN1170 BRISK-FL LiGHT SILIUS REFLECT CheckMate 459	ASCO 2011 AASLD 2012 ASCO-GI 2013 EASL 2016 Ongoing Ongoing	JCO 2013 JCO 2013 JCO 2015
	Second line	1. Brivanib vs. placebo[a] 2. Everolimus vs. placebo[a] 3. Ramucirumab vs. placebo[a] 4. S-1 vs. placebo[a] 5. Regorafenib vs. placebo[b] 6. Tivantinib vs. placebo 7. Ramucirumab vs. placebo 8. Pembrolizumab vs. placebo	BRISK-PS EVOLVE-1 REACH S-CUBE RESORCE JET-HCC REACH-2 KEYNOTE-240	EASL 2012 ASCO-GI 2014 ESMO 2014 ASCO 2015 WCGI 2016 Ongoing Ongoing Ongoing	JCO 2013 JAMA 2014 Lancet-O 2015

HAIC, hepatic arterial infusion chemotherapy. [a] RCT halted or with negative results. [b] RCT with positive results.

Current Status of the Development of Molecular Targeted Agents

Clinical trials are being conducted to develop molecular targeted agents for various stages of liver cancer, including the following: early-stage HCC, in which surgical resection or radiofrequency ablation is indicated; intermediate-stage HCC, in which transcatheter arterial chemoembolization (TACE) is indicated; and advanced-stage HCC, in which sorafenib is indicated.

Early-Stage HCC

The Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma (STORM) study, in which sorafenib was used to suppress HCC recurrence after curative therapy, revealed no difference in recurrence-free survival between the sorafenib and placebo groups, demonstrating that sorafenib was not efficacious at suppressing recurrence [3].

Peretinoin, an orally administered acyclic retinoid agent, is structurally similar to vitamin A and functions as a transcription activator and an inducer of differentiation. It is thought to remove precancerous HCC cells by inducing apoptosis and to inhibit carcinogenesis by promoting differentiation. A phase II/III study was launched to investigate the ability of peretinoin to suppress HCC recurrence, but the efficacy of peretinoin could not be evaluated due to problems with dosing [4]. A follow-up phase III trial has been initiated now that the dosing problems have been addressed (Table 1).

Intermediate-Stage HCC

Residual tumor and tumor recurrence are inevitable after TACE, because it is not a curative therapy. Since TACE can itself induce angiogenesis, the use of antiangiogenic agents after TACE greatly suppresses tumor recurrence and regrowth, and may even extend the duration of tumor suppression by TACE. This allows TACE to be performed less frequently, enabling preservation of liver function. Globally, many clinical trials have investigated the efficacy of sorafenib as a post-TACE adjuvant therapy. A study in Japan and Korea investigated time to progression (TTP) in patients treated with sorafenib after TACE but found that sorafenib did not prolong TTP in these patients [5].

In the SPACE study, a phase II study of sorafenib or placebo in combination with TACE with doxorubicin drug-eluting beads [6], the primary endpoint of TTP was achieved; however, the study outcome was considered negative because of the clinically insignificant difference between the sorafenib and placebo arms. Other large-scale studies, such as the Eastern Cooperative Oncology Group (ECOG) 1208 study and the TACE2 study, had to be discontinued due to insufficient enrollment. The outcome of the TACE2 study was reported in detail at the 2016 American Society of Clinical Oncology (ASCO) Annual Meeting [7]. The Transcatheter Arterial Chemoembolization Therapy in Combination with Sorafenib (TACTICS) study conducted in Japan is the only large-scale clinical trial that is currently underway. As shown in Table 1, negative outcomes have also been reported in studies with other agents, including the Brivanib versus Placebo as Adjuvant Therapy to Transarterial Chemoembolization in Patients with Unresectable Hepatocellular Carcinoma (BRISK-TA) study [8], a phase III study on brivanib (an inhibitor of vascular endothelial growth factor receptor [VEGFR] and fibroblast growth factor receptor [FGFR]), and the Orantinib in Combination with Transcatheter Arterial Chemoembolization in Patients with Unresectable Hepatocellular Carcinoma (ORIENTAL) study, a phase III study on orantinib (an inhibitor of VEGFR, platelet-derived growth factor receptor [PDGFR], and FGFR [9]).

Advanced-Stage HCC

Many trials have been conducted to develop molecular targeted agents that can replace sorafenib as a more potent and safe first-line therapy. However, the superiority or noninferiority of sunitinib, brivanib, and linifanib to sorafenib could not be proven [10–12]. A phase III study comparing lenvatinib and sorafenib has recently been concluded, and the results are eagerly awaited. The target molecules of lenvatinib are VEGFR1–3, FGFR1–4, RET, and c-Kit.

Clinical trials of brivanib, everolimus (an inhibitor of mTOR [mechanistic target of rapamycin]), and ramucirumab (a human monoclonal antibody against VEGFR2) were conducted with the aim of developing second-line agents for patients unresponsive to or intolerant of sorafenib, but they failed to show superiority to the placebo (Table 1) [13–15]. However, because ramucirumab was highly effective in a group of patients with elevated serum α-fetoprotein (AFP), a phase III study of ramucirumab is currently underway on patients with serum AFP levels ≥400 ng/ml. Recently, on June 30, 2016, positive data from the RESORCE study of regorafenib, an inhibitor of a broad range of kinases including VEGFR, PDGFR, FGFR, TIE2, Kit, RET, and RAF, were presented at the World Congress on Gastrointestinal Cancer (WCGC). As a groundbreaking result, overall survival (OS), the primary endpoint of the study, was significantly improved in patients that received regorafenib as a second-line therapy (median survival time: 10.6 months, vs. 7.8 months in the placebo group; hazard ratio: 0.62; 95% confidence interval: 0.50–0.78; $p < 0.001$) (Table 2). Importantly, the study design might have contributed to the positive outcome. First, the study included a group of patients who progressed while on sorafenib, but these patients were required to have received ≥400 mg of sorafenib for at least 20 of 28 days prior to enrollment in the RESORCE trial; patients who discontinued sorafenib due to poor tolerability were excluded. Second, vascular invasion and extrahepatic spread were treated as independent stratification factors because

104

Table 2. Results of the RESORCE trial

	Regorafenib	Placebo	HR (95% CI); *p* value
Subjects, *n*	379	194	
BCLC stage C, %	88	87	
Treatment duration, months	3.6 (0.03–29.4)	1.9 (0.2–27.4)	
OS, months	10.6	7.8	0.62 (0.50–0.78); *p* < 0.001
PFS, months	3.1	1.5	0.46 (0.37–0.56); *p* < 0.001
TTP, months	3.2	1.5	0.44 (0.36–0.55)
DCR, %	65.2	36.1	*p* < 0.001
ORR, %	10.6	4.1	*p* < 0.005
Adverse events grade ≥3, %	79.7	58.5	

BCLC, Barcelona Clinic Liver Cancer; OS, overall survival; PFS, progression-free survival; TTP, time to progression; DCR, disease control rate; ORR, overall response rate; HR, hazard ratio; CI, confidence interval.

Table 3. Imbalance between the brivanib and placebo arms

Demographic or characteristic	Brivanib (*n* = 263)		Placebo (*n* = 132)	
	n	%	*n*	%
Reason for sorafenib discontinuation				
Progression	227	86	116	88
Intolerance	35	13	16	12
Distant metastasis	171	65	84	64
Vascular invasion	81	31	24	18
Portal vein invasion and/or thrombosis	65	25	16	12

Cited and modified from Llovet et al. [13].

of the lessons learned from the failed brivanib trial (Table 3). As for other agents, a clinical trial of the c-MET inhibitor tivantinib is currently underway (Table 1).

Problems Associated with Clinical Trials of Molecular Targeted Agents for HCC

As stated above, numerous drug development trials ended with negative outcomes, and a number of potential reasons for these results have been proposed.

Problems Associated with the Heterogeneity of HCC

Compared with other types of cancer, HCC is very heterogeneous. In particular, HCC is a multicentric tumor, and its characteristics can vary from nodule to nodule, even within an individual patient. Consequently, the efficacy of molecular targeted agents is highly variable. Clinical trials use the Child-Pugh liver function score and the TNM tumor stage as inclusion criteria. Thus, a seemingly clinically homogeneous group of patients included in a study may actually be biologically heterogeneous. Therefore, to restrict the patient population to a biologically homogeneous group, drug development trials have started to rely on biomarkers [16]. A representative example is a trial of tivantinib, which inhibits the hepatocyte growth factor receptor c-MET [17]. This phase II study has shown the efficacy of tivantinib in patients with HCC expressing high levels of c-MET, even though in this group of patients, the prognosis is generally poor. Currently, a placebo-controlled phase III study is being conducted only on

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Kudo: Molecular Targeted Agents for Hepatocellular Carcinoma: Current Status and Future Perspectives

105

patients with tumors expressing high levels of c-MET. However, selecting patients based on biomarkers does not address the problem of tumor characteristics varying from nodule to nodule within the same patient. In other words, the possibility of sampling variability cannot be eliminated. Indeed, the outcome of a study using a mutation of RAS as a biomarker to investigate the efficacy of the MEK inhibitor refametinib was also unfavorable. These problems may be resolved once more effective serum biomarkers are identified. A phase II clinical trial of the TGF (transforming growth factor)-β receptor inhibitor galunisertib is currently underway, and improved OS and reduced TGF-β_1 levels in patients with normal AFP values were reported at the 2016 ASCO Annual Meeting [18].

Problems Associated with Stratification Factors

In general, stratification factors are stipulated to prevent bias during randomization. The proper handling of vascular invasion and extrahepatic spread is considered important in patients with HCC. The design of many ongoing clinical trials involves an allocation factor specifying "either vascular invasion or extrahepatic spread" or "neither vascular invasion nor extrahepatic spread." However, because vascular invasion is an extremely poor prognostic factor for HCC, assigning vascular invasion to the same category as extrahepatic spread may have influenced the outcome of clinical trials. In other words, if the active drug group contains more patients with vascular invasion while the placebo group includes more patients with extrahepatic spread, such a sampling bias will put the active drug groups at a disadvantage. In fact, this actually happened in a clinical trial of brivanib as second-line therapy (Table 3) [13]. In the RESORCE trial, which reported a positive outcome, patients were stratified separately by vascular invasion and by extrahepatic spread [19].

Influence of Post-Trial Treatment

Post-progression survival (PPS) is defined as the interval between a diagnosis of progressive disease and the patient's death; OS is expressed by the equation OS = PFS + PPS, where PFS is progression-free survival. Even when a statistical difference in PFS is observed, this might not be reflected in OS if PPS is sufficiently long. Indeed, OS correlated with PPS more strongly than with PFS in a clinical trial of sorafenib [20]. Locoregional therapy is the mainstay of treatment for HCC, but molecular targeted agents are indicated for cases where locoregional therapy is no longer practical. However, even after following the recommended therapeutic guidelines, locoregional therapy is often applied as a post-trial treatment, if the patient's general condition is stable. This rarely happens with other types of cancer and is an issue unique to HCC due to the availability of effective locoregional therapies such as intra-arterial infusion chemotherapy or TACE. It is therefore possible that if PPS is prolonged by effective post-trial treatments, there may be no significant difference in OS, the primary endpoint of the trial [21]. In addition, clinical trials of agents other than regorafenib use intolerability to sorafenib as an inclusion criterion; however, this is thought to augment the influence of post-trial treatments. Patients who progressed after administration of sorafenib are defined as unresponsive to sorafenib; they have a relatively advanced tumor burden and are in poor condition overall. By contrast, patients defined as intolerant to sorafenib, who discontinued the treatment due to adverse events, remain in a relatively stable condition. Clinically stable patients are more likely to be subjected to various post-trial treatments, particularly to locoregional therapy, regardless of whether they have received a second-line agent or a placebo during the trial. The outcome of a subanalysis of a phase II study of axitinib supports this contention. This analysis revealed that OS in the axitinib arm was much better than in the placebo arm when patients who discontinued therapy due to adverse events were excluded [22]. Taking this into consideration, clinical trials of second-line agents should enroll only those patients unresponsive to sorafenib, as was done in the RESORCE study [19].
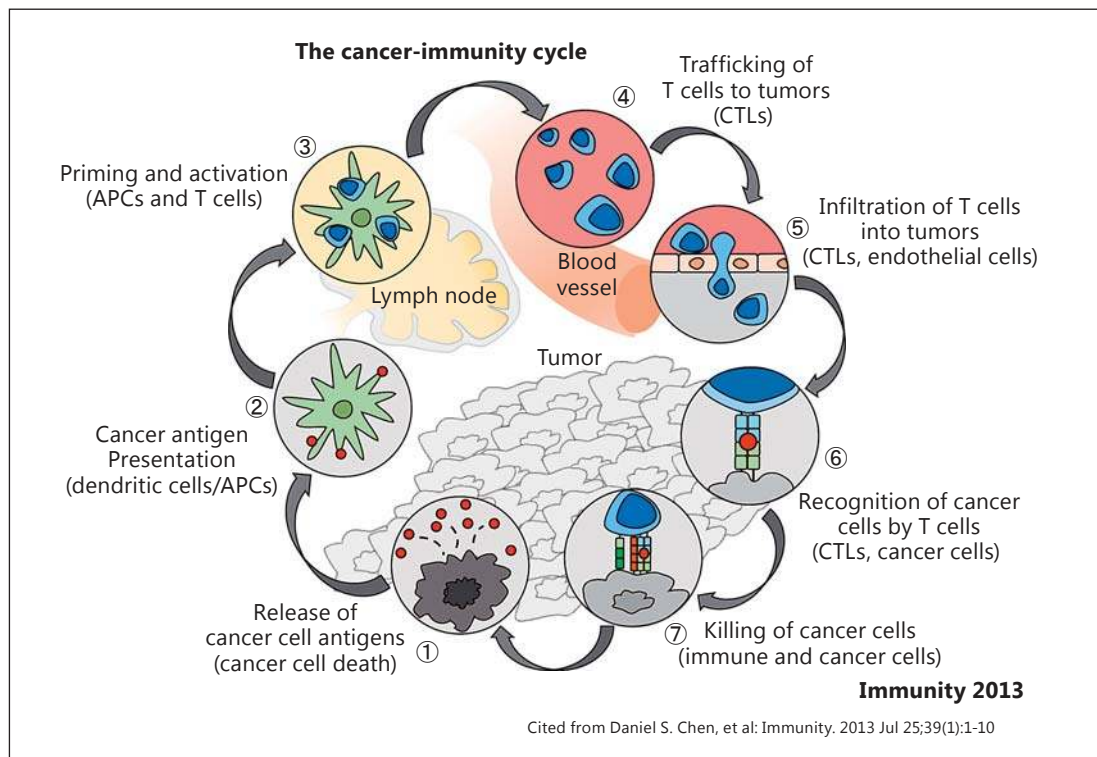
Fig. 1. The cancer-immunity cycle. Naïve T cells are activated by signals from antigen-presenting cells (APCs), which recognize the cancer cell antigens in the lymph node. At the tumor, activated T cells attack the cancer cells. CTLs, cytotoxic T lymphocytes.

As stated earlier, the clinical trial of regorafenib excluded patients intolerant to sorafenib. This decision was made primarily because regorafenib and sorafenib have similar toxicological profiles due to their structural similarity [19]. However, because patients intolerant to sorafenib were excluded, post-trial treatments were limited, resulting in a favorable outcome. This superior trial design resulted in a shorter PPS and therefore a greater difference in OS, clarifying the benefits of regorafenib therapy.

Hepatic Functional Reserve
Since many patients with HCC have an underlying chronic liver disease, such as cirrhosis, it is important to consider the effect of therapy on liver function. Most clinical trials enroll patients with Child-Pugh class A liver function (Child-Pugh score of 5–6 points). However, prognoses differ substantially between patients with a score of 5 and those with 6 points. Therefore, in the case of HCC, it may be necessary to include Child-Pugh scores of 5 and 6 as separate stratification factors.

Immune Checkpoint Inhibitors

An antibody against programmed cell death protein 1 (PD-1) has been gaining attention as an immune checkpoint inhibitor in recent years (Fig. 1–3). At the 2015 ASCO Annual Meeting, a phase I study of anti-PD-1 (nivolumab) in patients with HCC reported a favorable outcome, with 2 complete and 7 partial responses and an overall response rate of 19% [23].
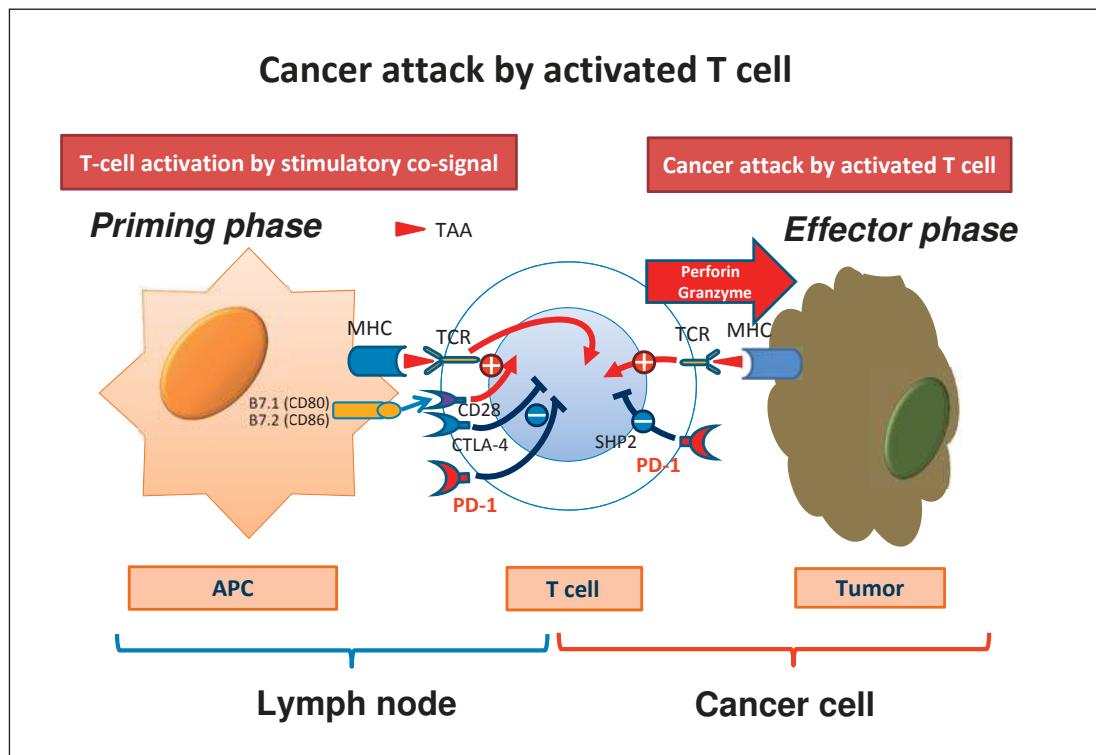
Kudo: Molecular Targeted Agents for Hepatocellular Carcinoma: Current Status and Future Perspectives

Fig. 2. After the recognition of tumor-associated antigen (TAA) by the T-cell receptor (TCR), a co-stimulatory signal by binding B7 and CD28, naïve T cells are activated. Consequently, the activated T cells attack the cancer cells by recognizing the TAA. Cancer cells are killed by activated T cells by producing perforin and granzyme. APC, antigen-presenting cell.

In Japan, a phase I/II study of nivolumab with dose expansion cohorts began in the summer of 2015. The outcomes of the dose escalation and dose expansion trials were reported at the 2016 ASCO Annual Meeting [24, 25] (Table 4). Furthermore, other reports included the design of a phase III clinical trial [26] and a study of combination therapy with anti-PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (Tables 5, 6) [27]. However, due to extremely expensive drug prices, it is very likely that the medical costs of these agents will strain nations' finances when approved for clinical use. Therefore, an urgent challenge today is to discover biomarkers that predict treatment response and thus offer a clear indication for their use.

Master Protocols

Drug development trials have high research and development costs and also require a huge effort to recruit participants. In the USA, the Lung Cancer Master Protocol (Lung-MAP) for patients with squamous cell lung cancer was launched in 2014 (Fig. 4) [28]. Patients were screened for alterations in cancer-related genes and were assigned to a trial arm best suited to each subject's genomic profile. This streamlined patient registration made the process more efficient, helping to reduce drug development costs. From the perspective of medical cost reduction, it may become possible to assign an appropriate agent to each patient. Clearly, this will be also extremely beneficial for patients with HCC and we await its early incorpo-
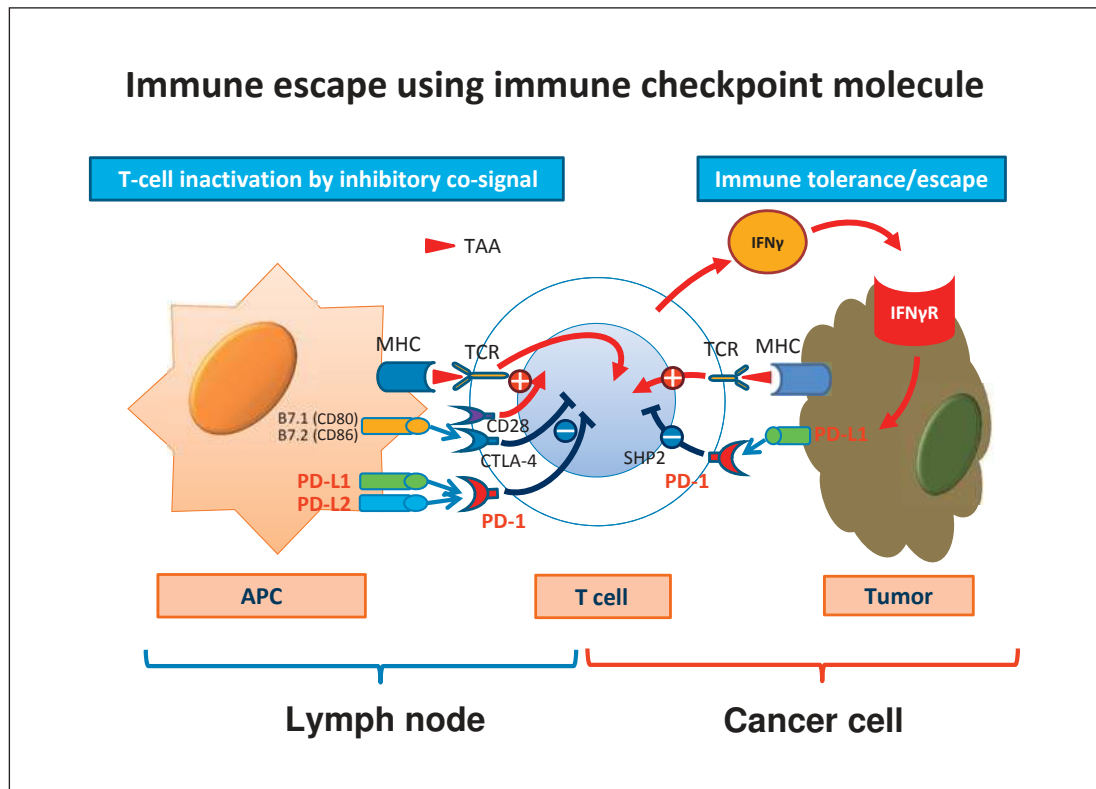
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Fig. 3. The immune checkpoint molecules PD-1, PD-L1, and CTLA-4 play an impact role in the cancer's escape from activated T cells (cancer immunotolerance/escape). APC, antigen-presenting cell; TAA, tumor-associated antigen; TCR, T-cell receptor.

Table 4. Objective response to nivolumab

	Uninfected: sorafenib naïve/ intolerant ($n = 54$)	Uninfected: sorafenib progressors ($n = 58$)	HCV ($n = 51$)	HBV ($n = 51$)	Total ($n = 214$)
Objective response	11 (20)	11 (19)	7 (14)	6 (12)	35 (16)
Partial response	0 (0)	2 (3)	0 (0)	0 (0)	2 (1)
Stable disease	32 (59)	27 (47)	29 (57)	23 (45)	111 (52)
Progressive disease	11 (20)	18 (31)	12 (24)	22 (43)	63 (29)
Not evaluable	0 (0)	2 (3)	3 (6)	0 (0)	5 (2)

Data are presented as n (%). Cited from El-Khoueiry et al. [25]. HCV, hepatitis C virus; HBV, hepatitis B virus.

ration. Such results could contribute substantially to the health care economy. Of course, this cannot be achieved by a single pharmaceutical manufacturer but requires the cooperation of multiple manufacturers. Public organizations should also be involved, so that this effort can be made within a public-private integrated project. In Japan, a similar project, SCRUM-Japan, was launched for patients with lung and gastrointestinal cancer including hepatobiliary and pancreatic cancer. Headed by the National Cancer Center, it is currently being tested at various institutions.

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Table 5. Current trials of immune checkpoint inhibitors

Drug	Trial name	Clinicaltrials.gov No.	Company	Phase	Subjects, n	Line of therapy	Design	Endpoint	Status
Nivolumab									
Nivolumab (PD-1 Ab)/ ipilimumab (PD-L1 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
Nivolumab (PD-1 Ab)	CheckMate 459	NCT02576509	ONO	III	726	1L	Nivolumab vs. sorafenib	TTP/OS	Recruiting
Pembrolizumab									
Pembrolizumab (PD-1 Ab)	KEYNOTE-224	NCT02702414	MSD	II	100	2L	Pembrolizumab (1 arm)	ORR	Completed
Pembrolizumab (PD-1 Ab)	KEYNOTE-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

Ab, antibody; BMS, Bristol-Myers Squibb; ONO, Ono Pharmaceutical Co., Ltd.; MSD, MSD K.K.; 1L, first line; 2L, second line; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; ORR, overall response rate; TTP, time to progression; OS, overall survival; PFS, progression-free survival.

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110

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Table 6. Clinical trials of CTLA-4 antibody in hepatocellular carcinoma

NCT No.	Agent	Design	Status	Subjects, *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 months Reduction in HCV viral load

RFA, radiofrequency ablation; PR, partial response; DCR, disease control rate; TTP, time to progression; HCV, hepatitis C virus.
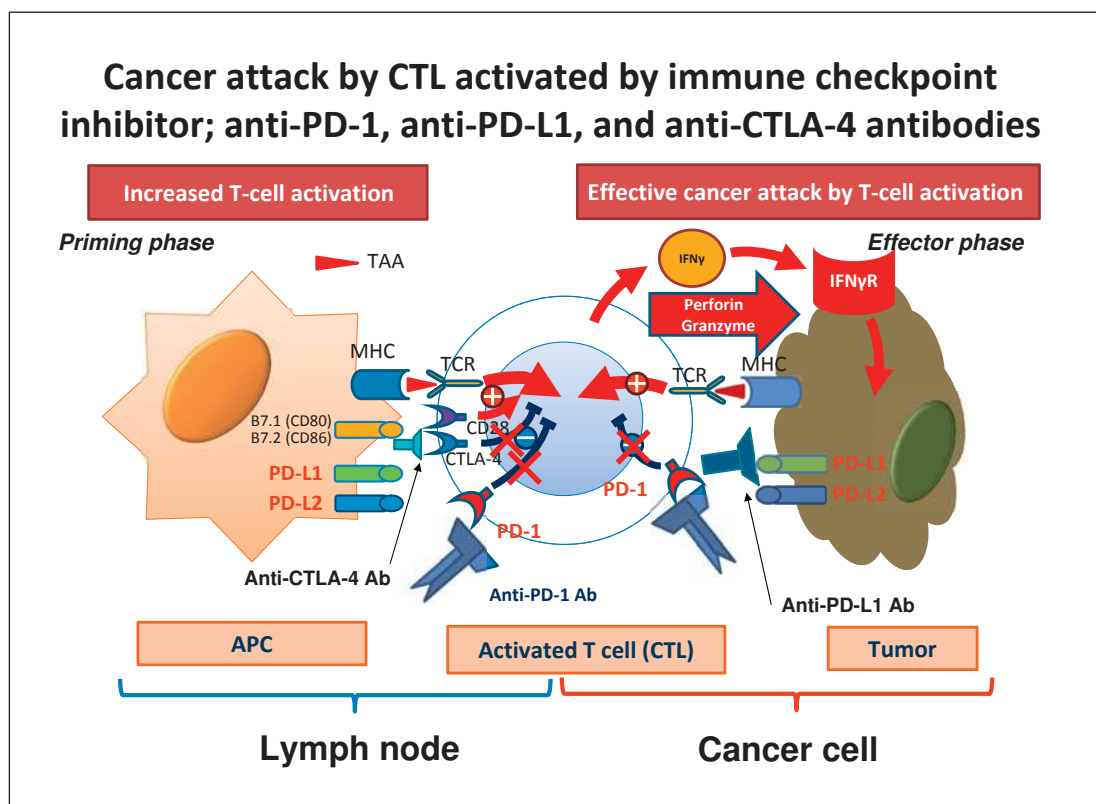

Fig. 4. Anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies restore T-cell activation, leading to an effective cancer attack by the immune system. APC, antigen-presenting cell; TAA, tumor-associated antigen; TCR, T-cell receptor; CTL, cytotoxic T lymphocyte.

Conclusion

Here, we reviewed the current development status of molecular targeted agents and future trends in drug development for HCC. Because of the difficulties involved in developing novel agents, the positive outcome obtained with regorafenib is exiting news and may change

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111

Kudo: Molecular Targeted Agents for Hepatocellular Carcinoma: Current Status and Future Perspectives

the treatment paradigm for HCC. While expectations are rising for immunotherapy, new patient selection criteria are also emerging based on biological homogeneity as determined by biomarkers. This differs from the conventional selection criteria based on liver function and TNM stage. Furthermore, to reduce medical costs, it is necessary to put drug development into a broader perspective by, for example, incorporating new concepts such as the master protocol system into clinical trials.

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Liver Cancer

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112

Kudo: Molecular Targeted Agents for Hepatocellular Carcinoma: Current Status and Future Perspectives

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