Editorial

Pembrolizumab for the Treatment of Hepatocellular Carcinoma

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Osaka-Sayama, Japan*Prof. M. Kudo* Editor *Liver Cancer* **Introduction**

Immune checkpoint inhibitors show promise for the treatment of hepatocellular carcinoma (HCC) as well as other types of cancer [1]. This editorial describes the role of pembrolizumab, an anti-programmed cell death protein 1 (PD-1) antibody, in the treatment of HCC.

Mechanism Underlying the Effect of Immune Checkpoint Inhibitors on Enhancing the Antitumor Immune Response

Tumor-associated antigens are released by tumor cells and subsequently bound by major histocompatibility complex molecules on the surface of immune-presenting cells. Upon binding, these cells migrate to lymph nodes and present the antigens to T cell receptors on immature T cells. Activation of immature T cells requires not only antigenic stimulation (signal 1), but also a costimulatory signal (signal 2). B7 molecules (CD80/B7-1 and CD86/B7-2 B2) expressed on antigen-presenting cells provide signal 2 by binding as ligands to CD28 on T cells. Then, T cells are activated and become CD8-positive activated T cells (priming

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phase). The blood circulation subsequently delivers CD8-positive activated T cells to the tumor vicinity. Here, they recognize tumor antigens presented by major histocompatibility complex molecules on tumor cells and attack these cells via molecules such as perforin and granzyme (effector phase). These steps constitute the well-known cancer immunity cycle, an anticancer immune response to tumor antigens.

Although the T cell attack is somewhat effective at first, its effect is soon lost because programmed death ligand 1 (PD-L1) is expressed on the surface of tumor cells by the action of interferon gamma, which is released concurrently with the T cell attack and contributes to tumor escape. Several studies examined therapies that enhance this antitumor immune response, such as peptide therapy, dendritic cell therapy, cytokine therapy, and lymphokine-activated killer cell therapy; however, few effective treatments have been established because the body's immune escape mechanism is not well understood. Immunostimulatory actions alone are not effective in theory or in practice because pressing the immune "accelerator" increases the efficacy of the immune "brake."

Immune Escape Mechanism of Cancer and Inhibitors of Immune Escape

There are two main immune escape mechanisms in the body, one mediated by lymph nodes and one at the cancer site.

CTLA4 Pathway and Inhibitors

CTLA4 is found mainly in lymph nodes, where it controls the proliferation of activated lymphocytes. CTLA4 is constitutively expressed in regulatory T cells (Tregs) and transiently expressed in a wide range of T cells in the early stages of activation (within 24–48 h). The affinity of CTLA4 for T cells that are activated via the B7/CD28 costimulatory pathway (signal 2) is ≥ 10 -fold greater than that of CD28. Therefore, CTLA4 competes with CD28 for binding to B7-1 and B7-2 molecules, transmitting an inhibitory signal 2 to the T cell. Under normal conditions, CTLA4 terminates T cell activity that is no longer physiologically necessary, thereby regulating excessive T cell immune responses. In cancer, however, CTLA4 acts as a brake, inhibiting the proliferation (activation and production) of T cells that have undergone tumor-associated antigen recognition. Anti-CTLA antibody therapy unlocks the brake mechanism that inhibits the activation of T cells in lymph nodes. Since CTLA4 is also strongly expressed in Tregs, decreased activation of Tregs in tumor sites may be one of the mechanisms underlying the antibody function of anti-CTLA4.

PD-1/PD-L1 Pathway and Inhibitors

The PD-1 molecule is an immunosuppressive accessory signal receptor that is expressed on activated T cells, B cells, and the myeloid cell series; it antigen-specifically inhibits T cell activity by binding to PD-L1 and PD-L2. PD-L1 and PD-L2 are expressed on dendritic cells, whereas PD-L1 is also widely expressed in blood vessels, the myocardium, lungs, and placenta.

PD-1 is rarely expressed in the peripheral blood of normal mice or healthy humans. It is expressed locally on T cells in the late stages of activation, e.g., after infection or an immune response such as inflammation. It is particularly strongly expressed on effector T cells of peripheral tissues.

In contrast to PD-1, PD-L1 is constitutively expressed in normal peripheral tissues. The activation of an immune response stimulates PD-L1 expression on most immunocompetent cells, including activated T and B cells. PD-L1 is also expressed on most tumor cells, as described below.

The expression of PD-L2 is limited to antigen-presenting cells, and it is involved only in the activation of T cells in lymph nodes. It is for this reason that anti-PD-1 and anti-PD-L1 antibodies have almost the same effects, whereas PD-L2 plays a limited role in cancer immunity.

After T cell receptors on activated T cells have recognized tumor antigens presented by tumor cell major histocompatibility complex molecules, the T cells release perforin and granzyme to attack the tumor. At the same time, T cells produce cytokines such as interferon gamma, which triggers the expression of PD-L1 molecules by nearby tumor cells as a protective mechanism, and PD-L1 molecules bind to PD-1. Then, signals that negatively affect tumor immunity are delivered to cytotoxic T cells, reducing T cell activity and resulting in immune escape or tolerance.

The administration of PD-1 antibodies such as pembrolizumab can unlock the immune “brake” mechanism, restoring the ability of the immune system to attack tumor cells. Unlike conventional chemotherapies and molecular-targeted therapies, PD-1 antibodies act on tumor cells by restoring the potent and accurate host immune system [2–13]. Antibodies to PD-L1 have the same effects [14]. PD-L1 acts as a biomarker for predicting the effects of anti-PD-1 antibody [15]. However, as the anti-PD-1 antibody is effective in some cases of HCC that do not express PD-L1, it cannot be used as a biomarker for HCC.

Pembrolizumab in HCC

Pembrolizumab is a strong, selective, IgG4/κ isotype humanized monoclonal antibody that directly inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2. It was approved for the treatment of melanoma, non-small-cell lung cancer, squamous cell carcinoma, gastric cancer, urothelial cancer, and classical Hodgkin lymphoma [16, 17]. Another monoclonal antibody, nivolumab, received the FDA’s accelerated approval on September 22, 2017 as a second-line agent for the treatment of HCC after sorafenib therapy based on the results of the CheckMate 040 phase I/II trial [18].

Similar to nivolumab, pembrolizumab received the FDA’s accelerated approval on November 10, 2018 as a second-line agent for the treatment of HCC after sorafenib therapy based on the results of the KEYNOTE-224 phase II trial [19]. The next section outlines the results of the KEYNOTE-224 trial and discusses the future outlook of HCC treatment.

KEYNOTE-224 Trial

Study Design

The KEYNOTE-224 trial was a nonrandomized, multicenter, open-label, phase II trial conducted in 47 centers in 10 countries, and it enrolled 104 subjects between June 7, 2016 and February 9, 2017. The main inclusion criteria were as follows: (1) histopathologically confirmed HCC, (2) previous treatment with sorafenib resulting in confirmed intolerance to sorafenib or radiographically confirmed progressive disease (PD), (3) Eastern Cooperative Oncology Group (ECOG) performance status 0–1, (4) Child-Pugh A cirrhosis, and (5) adequate organ function (Fig. 1).

Enrolled patients received 200 mg pembrolizumab intravenously once every 3 weeks for 2 years or until disease progression, unacceptable toxicity, patient withdrawal, or discontinuation of treatment based on the investigator’s discretion. The primary endpoint was the objective response (OR) rate (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) based on central review. Safety data were also collected (Fig. 1).

Fig. 1. Study design of KEYNOTE-224. BCLC, Barcelona Clinic Liver Cancer; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

Table 1. Response to pembrolizumab treatment

Best overall response	
Complete response	1 (1%)
Partial response	17 (16%)
Stable disease	46 (44%)
Progressive disease	34 (33%)
Objective response	18 (17%; 11–26)
Disease control	64 (62%; 52–71)
Median time to response, months (IQR)	2.1 (2.1–4.1)
Median duration of response, months (range)	not reached (3.1–14.6+)
Duration of response ≥9 months	12 (77%)

Efficacy Outcome

At the time of data cutoff on February 13, 2018, 17 (16%) subjects were still under treatment with pembrolizumab. The median duration of follow-up was 12.3 months (IQR 7.6–15.1). Of 104 subjects, 18 achieved an OR, and the overall response rate (ORR) was 17% (95% CI 11–26). Forty-six (44%) subjects had stable disease and 34 (33%) had PD (Table 1). The median time to response was 2.1 months (IQR 2.1–4.1). Of 18 responders, 12 (67%) reached a response at the time of the first imaging examination for efficacy during weeks 8–10. The median response duration was not reached (3.1–14.6+) and the response duration was favorable, i.e., ≥9 months in 12 (77%) subjects (Table 1).

At the time of data cutoff, 84 (81%) subjects had experienced death or PD, and the median progression-free survival (PFS) was 4.9 months (95% CI 3.9–8.0). Sixty (58%) subjects died before data cutoff, and the median overall survival (OS) was 12.9 months (95% CI 9.7–15.5) [19].

Table 2. Positivity of PD-L1-related biomarker (*n* = 52)

	Positive	Negative
CPS ¹	22 (42%)	30 (58%)
TPS ²	7 (13%)	45 (87%)

CPS, combined positive score; PD-L1, programmed death ligand 1; TPS, tumor proportion score. ¹ Number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages)/total number of viable tumor cells × 100. ² Percentage of viable tumor cells with partial or complete membrane staining of PD-L1 (≥1%) relative to all viable tumor cells present in the sample.

Table 3. Association of biomarkers with objective response

Objective response (confirmed best overall response)			<i>p</i> value
CPS ¹	positive (<i>n</i> = 22)	7 (32%)	0.021
	negative (<i>n</i> = 30)	6 (20%)	
TPS ²	positive (<i>n</i> = 7)	3 (43%)	0.088
	negative (<i>n</i> = 45)	10 (22%)	

CPS, combined positive score; PD-L1, programmed death ligand 1; TPS, tumor proportion score. ¹ Number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages)/total number of viable tumor cells × 100. ² Percentage of viable tumor cells with partial or complete membrane staining of PD-L1 (≥1%) relative to all viable tumor cells present in the sample.

Safety Profile

At least one adverse event (AE) was observed in 101 (97%) subjects. Treatment-related AEs (TRAEs) were observed in 76 (73%) subjects, of whom 16 (15%) experienced serious TRAEs. Grade 3 TRAEs were observed in 25 (24%) subjects, including elevation of aspartate aminotransferase in 7 (7%) subjects and fatigue in 4 (4%) subjects. A grade 4 TRAE, hyperbilirubinemia, occurred in 1 (1%) subject. One subject experienced treatment-related death from ulcerative esophagitis. Immune-mediated AEs were observed in 15 (14%) subjects, including hypothyroidism (8%) and adrenal insufficiency (3%). Grade 3 immune-mediated AEs included 2 cases of adrenal insufficiency, 1 case of severe skin toxicity, and 1 case of type 1 diabetes. Three (3%) subjects developed immune-mediated hepatitis, although no viral flare-ups of type B or C hepatitis were observed.

Predictive Biomarkers of OR

PD-L1 expression is an established predictor of pembrolizumab efficacy in other types of solid tumors, particularly non-small-cell lung cancer and stomach cancer. In addition, immune cell infiltration is associated with the clinical outcome of hepatic cancer [20].

In the present study, pathological tissue samples were collected from 52 of 104 enrolled subjects. The samples consisted of 47 archival samples and 5 newly obtained biopsy samples. The 52 subjects analyzed were not significantly different from the overall sample population

Fig. 2. Trial design of KEYNOTE-240. AFP, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; PD, progressive disease; PS, performance status.

because there were no differences in background factors or important prognostic factors such as alpha-fetoprotein, Barcelona Clinic Liver Cancer stage, ECOG performance status, extrahepatic spread, and macrovascular invasion. The ORR of these 52 subjects was 25% (13 of 52 patients), which was not markedly different from that of the overall sample (17%).

The relationship between PD-L1 expression-related biomarkers and response is shown in Tables 2 and 3. In the present study, two new indices were used as PD-L1 expression biomarkers. One was the combined positive score (CPS), calculated by dividing the number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) by the total number of viable tumor cells and multiplying by 100. The other was the tumor proportion score (TPS), calculated by dividing the number of PD-L1-expressing tumor cells ($\geq 1\%$) (based on partial or complete staining) by the total number of viable tumor cells and multiplying by 100. Of 52 subjects, 22 (42%) were CPS positive, whereas only 7 (13%) were TPS positive (Table 2). Thirteen (25%) subjects achieved an OR according to both the CPS and TPS assessments. The OR rate was significantly different between the CPS-positive ($n = 7/22$; 32%) and CPS-negative ($n = 6/30$; 20%) subjects ($p = 0.021$). Three (43%) out of 7 TPS-positive subjects and 10 (22%) out of 45 TPS-negative subjects achieved an OR, indicating no significant difference, which was probably related to the small number of cases ($p = 0.088$) (Table 3) [19].

Similarly, there was a significant difference in PFS between CPS-positive and CPS-negative subjects ($p = 0.026$), but not between TPS-positive and TPS-negative subjects ($p = 0.096$). These findings were consistent with those obtained with nivolumab and were considered to reflect the tumor heterogeneity of HCC associated with biopsy sampling [18].

Based on these findings, pembrolizumab was approved by the FDA as a second-line agent for the treatment of HCC patients who are intolerant or unresponsive to sorafenib.

Outline of the Phase III Trial Design (KEYNOTE-240)

Phase III trials of pembrolizumab are ongoing, including the KEYNOTE-240 trial (ClinicalTrials.gov identifier: NCT02702401) in the United States, Asia, Australia, Europe, and Japan.

Table 4. Updated results of a phase Ib trial of lenvatinib plus pembrolizumab in unresectable HCC (NCT03006926)

Parameter	Lenvatinib + pembrolizumab (n = 30)		
	mRECIST per IR	mRECIST per IIR	RECIST version 1.1 per IIR
Best objective response, n (%)			
Complete response	1 (3.3%)	3 (10.0%)	0
Partial response	12 (40.0%)	15 (50.0%)	16 (53.3%)
Stable disease	16 (53.3%)	10 (33.3%)	11 (36.7%)
Progressive disease	0	1 (3.3%)	2 (6.7%)
Unknown/not evaluable	1 (3.3%)	1 (3.3%)	1 (3.3%)
Unconfirmed ORR, n (%)	13 (43.3%)	18 (60.0%)	16 (53.3%)
95% CI	25.5–62.6	40.6–77.3	34.3–71.7
ORR, n (%)	11 (36.7%)	15 (50%)	11 (36.7%)
95% CI	19.9–56.1	31.3–68.7	19.9–56.1
Median DOR, months (95% CI)	6.9 (3.4–NE)	8.1 (6.9–12.4)	8.3 (3.8–11.0)
Median TTR for responders, months (95% CI)	2.8 (1.3–2.8)	1.4 (1.3–2.8)	3.4 (1.4–5.7)
Disease control rate, n (%)	29 (96.7%)	28 (93.3%)	27 (90.0%)
95% CI	82.8–99.9	77.9–99.2	73.5–97.9
Median PFS, months (95% CI)	9.7 (7.5–NE)	9.7 (5.3–13.8)	9.7 (7.7–NE)
Median TTP, months (95% CI)	11.6 (9.7–NE)	9.7 (9.7–14.0)	9.7 (7.7–NE)
Median OS, months (95% CI)		14.6 (9.9–NE)	
OS rate (95% CI)			
6 months		83.3% (64.5–92.7)	
12 months		59.8% (31.6–79.5)	

DOR, duration of response; HCC, hepatocellular carcinoma; IIR, independent imaging review; IR, investigator review; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression; TTR, time to response.

The KEYNOTE-240 trial was performed in 26 countries in Asia, Oceania, Europe, North America, and South America, and the results will be available in 2019. Its co-primary endpoints are PFS (RECIST 1.1) based on independent review and OS. Its secondary endpoints are ORR, duration of response, disease control rate, time to progression, safety, and tolerability. The trial design of KEYNOTE-240 is shown in Figure 2. In KEYNOTE-240, 408 subjects who were intolerant or unresponsive to sorafenib were assigned to the pembrolizumab group or the placebo group at a ratio of 2:1 and are undergoing image assessment every 6 weeks [21]. The stratification factors are region (Asia – excluding Japan – and regions other than Asia), macrovascular invasion (positive or negative), and alpha-fetoprotein (≥ 200 vs. < 200 ng/mL). The exclusion criterion is tumor infiltration of the main portal vein (Vp4) or inferior vena cava [21]. Positive results of this phase III trial would lead to the worldwide approval of pembrolizumab as a promising treatment option in addition to conventional molecular-targeted agents [22, 23]. However, striking news released by Merck on February 19, 2017 indicate that this trial did not meet its primary endpoint of prolonging PFS or OS compared with placebo plus best supportive care [24].

In the final analysis of the KEYNOTE-240 study, there was an improvement in OS for patients treated with pembrolizumab compared with placebo, but these OS results did not meet statistical significance per the prespecified statistical plan (HR = 0.78 [95% CI 0.611–0.998], $p = 0.0238$). Results for PFS were also favorable in the pembrolizumab arm compared with placebo, but did not reach prespecified statistical significance (HR = 0.78 [95% CI 0.61–

Fig. 3. Treatment strategy using immune checkpoint inhibitors. PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor.

Table 5. Results of immune checkpoint inhibitors and combination therapy

	Nivolumab (n = 214)	Pembrolizumab (n = 104)	Pembrolizumab + lenvatinib (n = 26)	Atezolizumab + bevacizumab (n = 73)	SHR-1210 + apatinib (n = 18)	Durvalumab + tremelimumab (n = 40)
ORR (95% CI)	20% (15–26)	17% (11–26)	53.3% (34.3–71.7)	32%	38.9%	25%
DCR (95% CI)	64% (58–71)	62% (52–71)	90%	77%	83.3%	57.5% (>16 weeks)
PFS, months (95% CI)	4.0 (2.9–5.4)	4.9 (3.4–7.2)	9.7 (7.7–NE)	14.9 (0.5–21.5)	7.2 (2.6–NE)	NA
OS, months (95% CI)	NR ¹	12.9 (9.7–15.5)	14.6 (9.9–NE)	NR	NR	NA
DOR, months	9.9 (8.3–NE)	≤9 (77%)	8.3 (3.8–11.0)	≥12 (26%)	NE	NA

DCR, disease control rate; DOR, duration of response; NA, not available; NE, not evaluable; NR, not reached; ORR, overall response rate (RECIST 1.1); OS, overall survival; PFS, progression-free survival. ¹ Nine months: 74%.

0.99], $p = 0.0209$). The prespecified p value was too strict because α was split for 2 interim analysis and coprimary endpoint of PFS. Although the trial did not meet its coprimary endpoint, both OS and PFS showed clinical meaningful improvement over placebo similar to the results shown in the KEYNOTE-224 trial.

Combination Immunotherapy with Pembrolizumab and Lenvatinib

Efficacy Results

The updated results of an open-label phase Ib study of combination therapy with pembrolizumab and lenvatinib [25, 26] were presented at the American Association for Cancer Research Annual Meeting on April, 2019, in Atlanta, GA, USA [27]. Thirty patients were evaluated for safety and efficacy; the response rate was 60.0%, and the disease control rate was

Fig. 4. Immunosuppressive microenvironment produced by VEGF. Figure modified from Voron et al. [31]. DC, dendritic cell; MDSC, myeloid-derived suppressor cell; TAM, tumor-associated macrophage; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

93.3% per modified RECIST by independent image review (Table 4). According to RECIST 1.1, the response rate was 53.3% and the disease control rate was 90.0%, which are the best results of PD-1/PD-L1 antibody-based monotherapy or combination therapy with CTLA4 antibody or other tyrosine kinase inhibitors/anti-vascular endothelial growth factor (VEGF) antibody therapy obtained to date (Table 5; Fig. 3). PFS was also a favorable 9.7 months based on both investigator review and independent image review [28].

Safety Profile

For lenvatinib, the median duration of treatment was 7.9 months (range, 1–17), and the median dose intensity was 7.81 mg/day (range, 2.3–12.0). The median relative dose intensity was 67.5% (range, 28.5–100). For pembrolizumab, the median duration of treatment was 7.3 months (range, 1–17), and the median dose intensity was 200 mg (range, 150–200) every 3 weeks. The median relative dose intensity was 100% (range, 75–100). The median follow-up durations were 16.7 months (95% CI 15.0–17.8) in part 1 and 8.1 months (95% CI 6.7–9.7) in part 2. No dose-limiting toxicities were reported in part 1 of the study. There were 4 (13.3%) fatal AEs during the study; 2 deaths were considered treatment-related (acute respiratory distress syndrome and intestinal perforation). Other grade 3 or greater AEs included hypertension in 7 (23.3%), aspartate aminotransferase increase in 5 (16.6%), diarrhea in 3 (10%), and weight loss in 2 (6.7%) patients. No unexpected AEs were observed.

Mode of Action of Combination Therapy with Pembrolizumab and Lenvatinib

The synergistic effects and mode of action of combining lenvatinib with pembrolizumab were demonstrated in animal studies [29, 30], and the rationale is as follows. Voron et al. [31] reported that VEGF-A released by tumors and the vascular endothelium at the

Fig. 5. Mechanism of synergistic effects of lenvatinib and anti-PD-1/PD-L1 antibodies. **a** Immunosuppressive microenvironment plus PD-1/PD-L1 immunosuppression. **b** Lenvatinib plus anti-PD-1/PD-L1 antibodies synergistically induce PD-1/PD-L1 blockade and inhibit the immunosuppressive microenvironment. PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; TAM, tumor-associated macrophage; Tregs, regulatory T cells; VEGF, vascular endothelial growth factor.

tumor site promotes the formation of various immune suppressive cells such as tumor-associated macrophages (TAMs), Tregs, or myeloid-derived suppressor cells, which creates an immunosuppressive microenvironment that induces tumor immune escape. These cells release immunosuppressive cytokines (e.g., IL-10 and TGF- β), which block dendritic cell maturation and inhibit natural killer cell activation as well as T cell activation and proliferation (Fig. 4). Based on this theoretical foundation, inhibition of VEGF with an anti-VEGF antibody and molecular-targeted agents, whose targets include VEGF, leads to (1) improved antigen presentation to dendritic cells, (2) promotion of T cell activation in the priming phase, and (3) improvement in trafficking and infiltration from the lymph nodes to the tumor site through the normalization of tumor vasculature. VEGF inhibition also results in (4) regulation of the humoral factors TGF- β and IL-10 through the suppression of the abovementioned cells such as Tregs, TAMs, and myeloid-derived suppressor cells at the tumor site, which corrects the inhibitory immune microenvironment of the tumor. Finally, (5) inhibition of checkpoint molecules through anti-PD-1/PD-L1 antibody therapy reverses the cancer immunity cycle, which then acts against the tumor, enabling activated T cells to effectively attack the tumor (Fig. 5). Preclinical studies of combination therapy with pembrolizumab and lenvatinib demonstrate that correction of the immune suppressive microenvironment of the tumor (e.g., TAMs and Tregs) decreases the production of TGF- β and IL-10, which downregulates the expression of genes such as *PD-1* and *Tim3*. This finding supports that proinflammatory cytokines such as IL-12 induce antitumor immunity (Fig. 5) [29].

A trial assessing pembrolizumab in combination with lenvatinib (LEAP-002) is currently ongoing as a phase III study [30] (NCT: 03713593). This combination is the most promising treatment approach among combination therapies using various immune checkpoint inhibitors and antiangiogenic agents [30] (Table 5; Fig. 3).

Pembrolizumab in Microsatellite Instability-High Solid Cancers

The extension of the indications of pembrolizumab to include microsatellite instability-high solid tumors has made an additional treatment option available for patients with HCC [32]. However, microsatellite instability-high tumors are not frequent in patients with HCC and are found in 2–3% of all HCC patients.

Conclusion

Pembrolizumab was approved by the FDA as a second-line agent after sorafenib therapy based on a single-arm phase II trial, KEYNOTE-224. A phase III study of pembrolizumab, KEYNOTE-240, as a second-line agent after sorafenib therapy recently reported negative results, which will be published in detail in the future congress and journal. However, the clinical benefit over placebo was observed similar to that observed in KEYNOTE-224. The effect of pembrolizumab in combination with lenvatinib is currently being assessed in a phase III study [30] (LEAP-002; NCT: 03713593). Therefore, the results of the LEAP-002 trial are eagerly awaited.

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References

- 1 Kudo M. Immune checkpoint blockade in hepatocellular carcinoma: 2017 update. *Liver Cancer*. 2016 Nov; 6(1):1–12.
- 2 Sznol M, Chen L. Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. *Clin Cancer Res*. 2013 Mar;19(5):1021–34.
- 3 Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature*. 2014 Nov;515(7528):563–7.
- 4 Shih K, Arkenau HT, Infante JR. Clinical impact of checkpoint inhibitors as novel cancer therapies. *Drugs*. 2014 Nov;74(17):1993–2013.
- 5 Philips GK, Atkins M. Therapeutic uses of anti-PD-1 and anti-PD-L1 antibodies. *Int Immunol*. 2015 Jan;27(1): 39–46.
- 6 Mahoney KM, Freeman GJ, McDermott DF. The Next Immune-Checkpoint Inhibitors: PD-1/PD-L1 Blockade in Melanoma. *Clin Ther*. 2015 Apr;37(4):764–82.
- 7 Harshman LC, Drake CG, Wargo JA, Sharma P, Bhardwaj N. Cancer immunotherapy highlights from the 2014 ASCO Meeting. *Cancer Immunol Res*. 2014 Aug;2(8):714–9.
- 8 Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. *Curr Opin Immunol*. 2012 Apr;24(2):207–12.
- 9 Merelli B, Massi D, Cattaneo L, Mandalà M. Targeting the PD1/PD-L1 axis in melanoma: biological rationale, clinical challenges and opportunities. *Crit Rev Oncol Hematol*. 2014 Jan;89(1):140–65.
- 10 Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med*. 2015 Jun;372(26):2509–20.
- 11 Droeser RA, Hirt C, Viehl CT, Frey DM, Nebiker C, Huber X, et al. Clinical impact of programmed cell death ligand 1 expression in colorectal cancer. *Eur J Cancer*. 2013 Jun;49(9):2233–42.
- 12 Ribas A. Tumor immunotherapy directed at PD-1. *N Engl J Med*. 2012 Jun;366(26):2517–9.
- 13 Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med*. 2013 Jul;369(2):134–44.

- 14 Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012 Jun;366(26):2455–65.
- 15 Gao Q, Wang XY, Qiu SJ, Yamato I, Sho M, Nakajima Y, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. *Clin Cancer Res*. 2009 Feb;15(3):971–9.
- 16 Merck Sharp & Dohme. KEYTRUDA (pembrolizumab) prescribing information. March, 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s015lbl.pdf (accessed May 17, 2018).
- 17 Sharma P, Allison JP. The future of immune checkpoint therapy. *Science*. 2015 Apr;348(6230):56–61.
- 18 El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017 Jun;389(10088):2492–502.
- 19 Zhu AX, Finn RS, Edeline J, Cattani S, Ogasawara S, Palmer D, et al.; KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol*. 2018 Jul;19(7):940–52.
- 20 Carone C, Olivani A, Dalla Valle R, Manuguerra R, Silini EM, Trenti T, et al. Immune Gene Expression Profile in Hepatocellular Carcinoma and Surrounding Tissue Predicts Time to Tumor Recurrence. *Liver Cancer*. 2018 Sep;7(3):277–94.
- 21 Finn RS, Chan SL, Zhu AX, Know JJ, Cheng AL, Siegel AB, et al. KEYNOTE-240: Randomized phase III study of pembrolizumab versus best supportive care for second-line advanced hepatocellular carcinoma. *J Clin Oncol*. 2017;35(suppl):abstract TPS4143.
- 22 Kudo M. Molecular Targeted Agents for Hepatocellular Carcinoma: Current Status and Future Perspectives. *Liver Cancer*. 2017 Feb;6(2):101–12.
- 23 Cucchetti A, Piscaglia F, Pinna AD, Djulbegovic B, Mazzotti F, Bolondi L. Efficacy and Safety of Systemic Therapies for Advanced Hepatocellular Carcinoma: A Network Meta-Analysis of Phase III Trials. *Liver Cancer*. 2017 Nov;6(4):337–48.
- 24 Merck Newsroom. Merck provides update on KEYNOTE-240, a phase 3 study of KEYTRUDA® (pembrolizumab) in previously treated patients with advanced hepatocellular carcinoma. <https://www.mrknewsroom.com/news-release/oncology/merck-provides-update-keynote-240-phase-3-study-keytruda-pembrolizumab-previous> (accessed February 19, 2019).
- 25 Kudo M. Extremely High Objective Response Rate of Lenvatinib: Its Clinical Relevance and Changing the Treatment Paradigm in Hepatocellular Carcinoma. *Liver Cancer*. 2018 Sep;7(3):215–24.
- 26 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018 Mar;391(10126):1163–73.
- 27 Ikeda M, Sung MW, Kudo M, et al. A phase 1b trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) in unresectable hepatocellular carcinoma (uHCC): updated results. Presented at the American Association for Cancer Research Annual Meeting on April 3, 2019 in Atlanta, Georgia.
- 28 Ikeda M, Sung MW, Kudo M, et al. A phase 1b trial of lenvatinib (LEN) plus pembrolizumab (PEM) in patients (pts) with unresectable hepatocellular carcinoma (uHCC). *J Clin Oncol*. 2018;36(suppl): abstract 4076.
- 29 Kato T, Bao X, Macgrath S, et al. Lenvatinib mesilate (LEN) enhanced antitumor activity of a PD-1 blockade agent by potentiating Th1 immune response. *Ann Oncol*. 2016;27(suppl 6):2PD.
- 30 Kudo M. Combination Cancer Immunotherapy in Hepatocellular Carcinoma. *Liver Cancer*. 2018 Mar;7(1):20–7.
- 31 Voron T, Marcheteau E, Pernot S, Colussi O, Tartour E, Taieb J, et al. Control of the immune response by pro-angiogenic factors. *Front Oncol*. 2014 Apr;4:70.
- 32 Merck Newsroom. FDA approves Merck's KEYTRUDA® (pembrolizumab) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors. <https://www.mrknewsroom.com/news-release/prescription-medicine-news/fda-approves-mercks-keytruda-pembrolizumab-adult-and-pediatric> (accessed May 25, 2017).