Perspective

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Immunotherapy prototype Mark 3.0 model in primary liver cancer: adding locoregional stereotactic therapy and prognostic factors classification management

https://doi.org/10.1515/mr-2022-0045
Received December 10, 2022; accepted December 22, 2022;
published online January 24, 2023

Abstract: Immune checkpoint inhibitors (ICIs) like programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitor have shown considerable efficacy in several important cancers including primary liver cancer (PLC) like hepatocellular carcinoma and cholangiocarcinoma. However, only some patients with PLC will benefit, so combination therapy and biomarker classification detected by next-generation sequencing or immunohistochemistry are very important. Herein, we briefly summarize ICI-based therapies and stratify these evolving therapies for advanced PLC into three stages of immunotherapies Mark (Mk.) 1.0, 2.0, and 3.0. We illustrated the significance of ICI monotherapy (Mk. 1.0), offering combinational approaches with traditional strategies (Mk. 2.0) and additional locoregional therapy (Mk. 3.0) to achieve longer survival and even meet the "No Evidence of Disease" status. We also highlight the importance of biomarkers and prognostic factors for patients with advanced PLC treated with ICI-based therapies. Multidisciplinary team management should be investigated and collaborated closely to manage adverse events and sequential therapy suggestions for patients.

Keywords: hepatocellular carcinoma; immune checkpoint inhibitors; primary liver cancer; prognostic factors; programmed cell death-1; stereotactic therapy.

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Primary liver cancer (PLC), such as hepatocellular carcinoma (HCC) and main components of biliary tract cancers (BTC), is a common cancer worldwide and many patients are diagnosed with advanced disease [1, 2]. The tumor microenvironment, including cancer cells, stroma cells and extracellular matrix, in liver cancer is immunosuppressive, complex and heterogeneous. Advanced phased PLC is insensitive to traditional systematic therapy, so new treatment paradigms are urgently needed [1–3].

Immune checkpoint inhibitors (ICIs) work by blocking immune escape mechanisms and restoring immunity against tumors [1, 2]. These innovative drugs have been demonstrated to have considerable efficacy in practice and may result in enduring responses in several important cancers including PLC. Programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitor monotherapy has been approved for longer survival in certain cancer patients, but only some patients with PLC will benefit and have considerable duration of response (DOR) if responses [1, 2]. In recent years, ICI-based combination therapy, such as combinational immunotherapy, immunostimulant chemotherapies and locoregional treatments have resulted in increasing numbers of patients with advanced PLC improving and in some instances even meeting the "No Evidence of Disease (NED)" status.

However, because of the delays in guideline updates given ongoing randomized clinical trials, many patients with advanced PLC may not qualify for such combinational approaches. Herein, we briefly summarize ICI-based therapies and stratify these evolving therapies for advanced PLC into three stages of immunotherapies Mark (Mk.) 1.0, 2.0, and 3.0. We highlight the significance of ICI monotherapy (Mk. 1.0), offering combinational approaches with traditional strategies (such as chemotherapy/anti-angiogenesis approaches in Mk. 2.0) and additional locoregional therapy (in Mk. 3.0) (see Table 1). We also highlight the importance of biomarker and prognostic factors for patients with advanced PLC.

Table 1: Key immunotherapy prototype 1.0, 2.0, 3.0 trials of PD-1/PD-L1-based therapy in advanced primary liver cancer.

Study	Therapy	Study design	CR (RECIST 1.1)	PR (RECIST 1.1)	DOR	PFS	OS	≥ Grade 3 AE rate
Immunotherapy Mk. 1.0: Era of PD-1/PD-L1 monotherapy								
Checkmate-459 [4]	Nivolumab vs. sorafenib	First line; Advanced HCC; Phase 3 RCT; n = 371 vs. 372	4% vs. 1%	12% vs. 6%	23.3 vs. 23.4m	3.7 vs. 3.8 m (HR = 0.93, 95% CI, 0.79–1.10, p > 0.05)	16.4 vs. 14.8 m (HR = 0.85, 95% CI, 0.72–1.00, p = 0.0522)	Grade 3-4 TRAE 22% vs. 49%
Keynote-240 [5]	Pembrolizumab vs. placebo	Second-line; Advanced HCC; Phase 3 RCT; n = 278 vs. 135	2.2% vs. 0	16.2% vs. 4.4%	13.8m vs. not reached	3.0 vs. 2.8 m (HR = 0.718, 95% CI, 0.570–0.904, p = 0.0022 > 0.002)	13.9 vs. 10.6 m (HR = 0.781, 95% CI, 0.611–0.998, p = 0.0238 > 0.0174)	Grade ≥ 3 AE: 52.7% vs. 46.3%
Keynote-158 [6]	Pembrolizumab	Second-line; Advanced BTC; Phase 2 study; n = 104	0	5.8%	NR (range: 6.2–26.6+)	2.0 m	7.4 m	Grade 3-5 AE: 13.5%
Keynote-158-MSI [2]	Pembrolizumab	Second-line; Advanced Chol-angiocarcinoma with dMMR/MSI-H; Phase II single arm study; n = 22	9.1%	31.8%	NR: not reached	4.2 m0	24.3 m	Grade 3-4 TRAE: 14.6% in all cohort (n = 233)
Immunotherapy Mk. 2.0: Era of PD-1/PD-L1-based combination systemic therapy								
IMbrave-150 [1]	Atezolizumab + Bevacizumab vs. sorafenib	First line; Unresectable HCC; Phase 3 RCT; n = 336 vs. 165	8% vs. <1%	22% vs. 11%	Longer than 18 m: 51% vs. 22%	6.9 vs. 4.3 m (HR = 0.65, 95% CI, 0.53–0.81, p < 0.001)	19.2 vs. 13.4 m (HR = 0.66, 95% CI, 0.52–0.85, p < 0.001)	Grade 3-4 AE 63% vs. 57%
LEAP-002 study [7]	Lenvatinib + pembrolizumab vs. Lenvatinib + placebo	First line; Unresectable HCC; Phase 3 RCT; N = 395 vs. 399	1.5% vs. 1.5%	24.6% vs. 16.0%	16.6 vs. 10.4 m	8.2 vs. 8.0 m (HR = 0.867, 95% CI, 0.734–1.024, p = 0.0466)	21.2 vs. 19.0 m (HR = 0.840, 95% CI, 0.708–0.997, P = 0.0227 > 0.0185)	Grade 3-4 TRAEs: 61.5% vs. 56.7%
HIMALAYA study [8]	Tremelimumab + durvalumab (T300 + D) vs. durvalumab (D) vs. sorafenib (S)	First line; Unresectable HCC; Phase 3 RCT; n = 393 vs. 389 vs. 289	T300+D: 3.1% D: 1.5% S: 0	T300+D: 17.0% D: 15.4% S: 5.1%	T300+D:22.34m D:16.82m S: 18.43m	T300+D: 3.78 m (vs. S: HR = 0.90, 95% CI, 0.77–1.05) D: 3.65m (vs. S: HR = 1.02, 95% CI, 0.88–1.19) S: 4.07 m	T300+D: 16.56m (vs. S: HR = 0.78, 96.0% CI, 0.65–0.93, p = 0.0035) D: 16.56m (vs. S: HR = 0.86, 95.7% CI, 0.73–1.03, non-inferiority margin, 1.08) S: 13.77 m	Grade 3-4 TEAE T300+D: 50.5% D: 37.1% S: 52.4%

Table 1: (continued)

Study	Therapy	Study design	CR (RECIST 1.1)	PR (RECIST 1.1)	DOR	PFS	OS	≥ Grade 3 AE rate
TOPAZ-1 trial [9]	Durvalumab + Gemcitabine and Cisplatin vs. Placebo + Gemcitabine and Cisplatin	First-line; Advanced BTC; Phase 3 RCT; n = 341 vs. 344	2.1% vs. 0.6%	24.6% vs, 18.1%	6.4 vs. 6.2 m	7.2 vs. 5.7 m (HR = 0.75, 95% CI, 0.63–0.89, p = 0.001)	12.8 vs. 11.5 m (HR = 0.80, 95% CI, 0.66–0.97, p = 0.021)	Grade 3–4 AE: 75.7% vs. 77.8%
Lin et al. [10]	Lenvatinib + Pembrolizumab	Second-line and above; advanced BTC; single-arm study; n = 32	0	25%	NA	4.9 m	11.0 m	Grade 3-4 AE: 62.5%
Jian et al. [11]	Toripalimab, lenvatinib and Gemcitabine plus oxaliplatin	First-line; Advanced intrahepatic cholangiocarcinoma; Single-arm, phase 2 trial; n = 30	3.3%	76.7%	9.8m	10.0m	12 m OS rate: 73.3%	Grade 3–4 AE: 43%
Immunotherapy Mk. 3.0: Era of adding locoregional therapy plus PD-1/PD-L1 inhibitor together with systematic therapy								
Cai et al. [12]	TACE + Lenvatinib + PD-1 inhibitor vs. TACE + Lenvatinib	Many lines; Advanced HCC; Retrospectively n = 41 vs. 40	mRECIST: 9.8% vs. 2.5%	mRECIST: 46.3% vs. 30.0%	NA	7.3 vs. 4.0 m (HR = 0.43, p = 0.001)	16.9 vs. 12.1 m (HR = 0.48, p = 0.008)	Grade 3, 36.6% vs. 32.5%,
Wang X et al. [13]	HAIC + Bevacizumab + toripalimab	First-line; Advanced BTC; Single-arm, phase 2 trial; n = 32	3.1%	81.3%	NA	6 m PFS rate: 80.7%	12 m OS rate: 80.4%	Grade 3/4 AEs: 31.3%

HCC, hepatocellular carcinoma; BTC, biliary tract cancers; RCT, Randomized controlled trail; HR, hazard ratio; CI, confidence interval; CR, complete remission; PR, partial responses; m, month; DOR, duration of response; PFS, progression-free survival; OS, overall survival; NR, not reached; AE, adverse events; TRAE, treatment-related adverse events; TEAE, treatment-emergent adverse events; dMMR, mismatch repair deficiency; MSI-H, microsatellite instability-high; TACE, trans-arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, Modified RECIST; Mk, Mark.

Immunotherapy Mark (Mk) 1.0: era of PD-1/PD-L1 monotherapy

Several single-arm studies of PD-1/PD-L1 inhibitors have shown promising objective response rates (ORRs) (15%–20%) in HCC, but still show low ORRs and disease control rate (DCR) in BTC. Moreover, the DCR is not high for PD-1/PD-L1 monotherapy in all advanced PLC [1, 2]. However, for the microsatellite instability (MSI)-high/mismatch repair deficiency (dMMR) or tumor mutation burden (TMB)-high subtype which can be detected by next-generation sequencing (NGS) or immunohistochemistry (IHC) of cholangiocarcinoma (explored in the KEYNOTE-158 study), these PD-1 inhibitors show an ORR of approximately 40% and considerable DOR [2].

Immunotherapy Mk. 2.0: era of PD-1/PD-L1-based combination systemic therapy

We propose that Immunotherapy Mk. 2.0 refers to PD-1/PD-L1-based combination systemic therapy – immunogenic cell death etc. For unresectable hepatocellular carcinoma, a randomized controlled study (IMbrave 150) found the PD-L1 inhibitor atezolizumab with anti-vascular endothelial growth factor antibody bevacizumab has a better ORR (27.3% vs. 11.9%, p<0.001) and significantly prolonged updated progression-free survival (PFS; 6.9 vs. 4.3 months, hazard ratio [HR]=0.65, 95% confidence interval [CI], 0.53–0.81, p<0.001), overall survival (OS; 19.2 vs. 13.4, HR=0.66, 95% CI, 0.52–0.85, p<0.001) and the rates of grade 3 or 4 (56.1% vs. 55.1%) adverse events were similar between the two groups [1]. On the other hand, the recent phase 3 randomized controlled LEAP-002 study compared an oral multikinase inhibitor lenvatinib plus pembrolizumab with lenvatinib plus placebo for patients with first-line uHCC. LEAP-002 study proved that lenvatinib plus pembrolizumab did not significantly increase OS (21.2 vs. 19.0 months, HR=0.84, p=0.0227>0.0185) but led to the longest OS in patients with uHCC [7].

For patients with advanced BTC, the phase 3 TOPAZ-1 trial evaluated PD-L1 inhibitor durvalumab plus gemcitabine plus cisplatin chemotherapy. TOPAZ-1 trial revealed that durvalumab plus chemotherapy group have better OS (12.8 vs. 11.5 months, HR=0.80, 95%CI, 0.66–0.97; p=0.021), 24-month OS rate (24.9% vs. 0.4%) and mPFS (7.2 vs. 5.7 months, HR=0.75, p=0.001) and higher ORR (26.7% vs. 18.7%) than placebo plus chemotherapy group. Meanwhile, grade 3 or four adverse events (AEs) rate was similar (67.2% vs. 64.9%) between the two groups [9]. We also found that pembrolizumab plus lenvatinib offers considerable ORR and 78.1% DCR in patients with chemotherapy-refractory BTC [10]. Recently, the PD-1 inhibitor toripalimab and lenvatinib with gemcitabine plus oxaliplatin (GemOx) chemotherapy has been shown to have ORR greater than 80% and DCR of 93.3% for first-line 30 patients with advanced intrahepatic cholangiocarcinoma (ICC), and these median PFS and OS were both not reached for short-term follow-up [11].

In this scenario, the ORR can be further improved, and the PR rate ranges from 27.3% to 80%, but the complete remission (CR) rate remains quite low (<10%). Patients who show partial responses (PR) to ICI-based therapy and do not convert to CR will eventually develop into anti-PD-1 refractory status. Therefore, it is very important to add locoregional therapy to convert such a partial “in limbo” status into CR status, or even reach NED status.

Immunotherapy Mk. 3.0: era of adding locoregional therapy plus PD-1/PD-L1 inhibitor together with systematic therapy

Although PD-1/PD-L1-based treatments with combinational systemic therapy have shown some promising efficacy, additive locoregional therapies, such as trans-arterial chemoembolization (TACE), radiofrequency ablation, hepatic arterial infusion chemotherapy (HAIC), and radiotherapy (Immunotherapy Mk. 3.0), may fully activate the immune response, control tumor burden, and slow down the pace of progression, which makes some cold tumors easier to respond, thus providing additional benefits in patients with PLC.

According to a randomized controlled study for patients with uHCC (n=338), lenvatinib plus TACE have a higher ORR (54.1% vs 25.0%), a longer median PFS (10.6 vs. 6.4 months; HR=0.43, p<0.001), and longer median overall survival (17.8 vs. 11.5 months [HR=0.45, p<0.001]) than the lenvatinib monotherapy group. Moreover, in the lenvatinib plus TACE group, 26 patients (15.3%) was downstage to curative surgical resection, while only 3 patients (1.8%) in the lenvatinib group underwent resection [14]. A retrospective study with 81 consecutively uHCC patients indicated that the pembrolizumab + lenvatinib + TACE group could achieve significantly longer OS and PFS than the lenvatinib + TACE group [12]. Our team also discovered 9 uHCC patients with oligometastases, using combinational stereotactic immunotherapy Mk.

3.0 strategy even could achieve downstaging converse surgery to long NED survival [15].

In unresectable ICC, a single-arm study illustrated that hepatic arterial infusion of floxuridine plus systemic GemOx chemotherapy resulted in 58% of ORR and 84% of DCR. The median PFS and OS were 11.8 and 25.0 months respectively [16]. Recently, a small prospective advanced BTC cohorts (n=32) that received HAIC and bevacizumab in combination with PD-1 inhibitor toripalimab could achieve 84.3% ORR and 96.9% DCR [13].

Moreover, some patients with unresectable PLC could be downstaged and become eligible for resection (conversion surgery) in the cohort [14–16]. For patients with oligometastases, it is prioritized to receive effective systemic therapy, then followed by locoregional therapy to control tumor burden, which may lead to long-term local control and PFS.

In this new and exciting era, we hope to add locoregional therapy to PD-1/PD-L1-based systemic combinational therapy to improve local control, increase the ORR and extend the PFS and overall durations of response and survival. We believe it is important to convert PR status to CR status through early active locoregional therapy, as in combinational Mk. 3.0 ICI. The current data in our center are encouraging. Of course, for patients with initiated stable disease (SD) status after ICI-based therapy, adjusting the systemic therapy strategy and adding locoregional therapy may help achieve PR to even CR status. Important phase 2/3 randomized studies (NCT04246177/NCT03778957/NCT04224636/NCT04340193/ChiCTR1900027102) for unresectable HCC are ongoing to investigate this issue.

Stratification management based on biomarker and prognostic factors and NGS applying

From the immunotherapy 1.0 to 2.0 to 3.0 era, it is clear that just some patients will achieve long benefits [1, 2], so biomarker and prognostic factors of immunotherapy for PLC will be very important. PD-L1 expression of tumor tissue IHC is very important.

For patients with uHCC treated with nivolumab, patients with tumor PD-L1≥1% have a better survival trend of mOS (28.1 vs. 16.6 months, p=0.03) than that of tumor PD-L1<1% [17]. Some genomic features like pre-existing immunity (high expression of CD274, T-effector signature and intratumoral $CD8^+$ T cell density) based on NGS were associated with better clinical outcomes with the combination of atezolizumab and bevacizumab [18]. For BTC patients, NGS could also reveal more potential therapeutic targets (like FGFR2 fusion, IDH1 R132C mutation, MSI-H, and PD-L1 Expression) to match related precision medicine. Our team also found that plasma cell-free DNA copy number variations based on NGS may predict the efficacy of immunotherapy in patients with advanced PLC [3].

On the other hand, prognostic factors of immunotherapy need to be noticed in real-world practice. Our previous study enrolled 378 uHCC patients who were treated with lenvatinib plus PD-1 inhibitors found Child-pugh grade (A vs. B), Eastern Cooperative Oncology Group (ECOG) score (0 vs. 1–2), Barcelona Clinic Liver Cancer stage (B vs. C) and achieve response (yes vs. no) were the prognostic factors for both longer OS and PFS [19].

Dilemmas and prospects

We propose that the curative era for advanced cancer is fast approaching with the development of these innovative “Mk. 3.0” developments in immunotherapy. However, many dilemmas also remain in the immunotherapy Mk. 3.0 for patients’ treatment. First, the data corresponding to the combination locoregional therapy with systemic therapy remains insufficient. Various phase 1/2 combination therapies show promising efficacy, but there remains a lack of confirmed results of phase 3 studies. Therefore, it is difficult to choose specific treatments. Second, considering superimposed adverse events and the cost-effectiveness of combination therapy, patients’ selection, management of adverse events, and optional time to locoregional intervention, multidisciplinary team management must also be investigated and collaborated closely.

It is very important to choose the right patient for stratified management in real-world practice. For locally advanced PLC patients with good ECOG scores and preserved liver function, the early addition of locoregional therapy to systemic therapy may confer better efficacy, downstaging and conversion to surgery, thereby leading to NED status and long-term survival. The future is already here, as combinational stereotactic immunotherapy may be applicable to nearly all patients with advanced cancer, inclusive of PLC.

Acknowledgment: We thank Prof. Simon C. Robson from the Center for Inflammation Research, Department of Anesthesia, Beth Israel Deaconess Medical Center, Harvard Medical School to revise and edit this manuscript.
Research funding: This work was supported by National High Level Hospital Clinical Research Funding [2022-

PUMCH-B-128], CAMS Innovation Fund for Medical Sciences (CIFMS) [2022-I2M-C&T-A-003][2021-I2M-1-061][2021-I2M-1-003], CSCO-hengrui Cancer Research Fund [Y-HR2019-0239][Y-HR2020MS-0415][Y-HR2020QN-0414], CSCO-MSD Cancer Research Fund [Y-MSDZD2021-0213] and National Ten-Thousand Talent Program.

Author contributions: HZ and XuY contributed to the conception of this perspecitive. HZ, XuY, NZ, YS, XY and XS performed the literature review and interpretation. All authors contributed to the writing of the manuscript and approved the final version.

Competing interests: Not applicable.

Ethical approval: Not applicable.

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