LUPINE PUBLISHERS
Open Access

Open Access Journal of Oncology and Medicine

DOI: 10.32474/OAJOM.2018.01.000109

ISSN: 2638-5945

Editorial

What is beyond the Nivolumab Monotherapy approval for advanced Hepatocellular Carcinoma?

Luis Mendoza*

Senior Medical Advisor, IQVA, Europe

Received: March 21, 2018; **Published:** March 26, 2018

***Corresponding author:** Luis Mendoza, Senior Medical Advisor Medical Strategy & Science, Oncology-Hematology, Therapeutic Science & Strategy Unit, IQVA

Keywords: Hepatocellular carcinoma; Immune checkpoint inhibitors; Nivolumab; FDA

Editorial

With an estimated 500,000 new cases per year, hepatocellular carcinoma (HCC) represents the third leading cause of cancer death worldwide. The incidence is rising in the west, largely due to an increasing incidence of hepatitis C virus infection [1]. The majority of HCC patients are diagnosed with disease too advanced for curative treatment. Only liver resection and liver transplantation are considered curative, with poor efficiency of other modalities such as radiofrequency ablation (RFA) and transarterial chemoembolization (TACE), although this may provide a modest prolongation in survival; however, the relapse in the majority of these patients is inevitable [2]. An array of translational research and pilot clinical trials have revealed that adoptive immunotherapy's are safe by patients with HCC, but they lack efficacy [3]. Now, we are in the new era of immunotherapy's such as immune checkpoint inhibitors and CAR-T strategies, which would bring benefit to the HCC patients.

On September 22, 2017, the Food and Drug Administration granted accelerated approval to nivolumab (OPDIVO, Bristol-Myers Squibb Co.) for the treatment of HCC in patients who have been previously treated with sorafenib. The approval was based on a 154-patient subgroup of CHECKMATE-040 (NCT 01658878), a multicenter, open-label trial conducted in patients with HCC and Child-Pugh. A cirrhosis who progressed on or were intolerant to sorafenib. Patients received nivolumab 3 mg/kg by intravenous infusion every two weeks. The confirmed overall response rate, as assessed by blinded independent central review using RECIST 1.1, was 14.3% (95% CI: 9.2, 20.8), with three complete responses and 19 partial responses. The response duration ranged from 3.2 to 38.2+ months; 91% of responders had responses lasting six months or longer and 55% had responses lasting 12 months or longer. Adverse reactions occurring in patients with HCC in CHECKMATE-040 were similar to those previously reported in product labelling, with the exception of a higher incidence of elevations in transaminases and bilirubin levels [4].

There are other immune checkpoint inhibitors that are being tested as monotherapy for efficacy and safety in HCC. Nivolumab was the first approved, but others will follow, as it has occurred in other malignancies. There is a bunch of possibilities for the treatment strategy using immune checkpoint inhibitors. Future directions point to various stages of HCC treatment, such as neo adjuvants and adjuvants after resection and ablation, combination therapy with transcatheter arterial chemoembolization, first-and second-line treatments, and all sorts of combinations with other immunotherapies, targeted molecules and novel therapies.

In the table annexed to this editorial you will find a list of ongoing clinical trials combining the immune checkpoint inhibitors with other therapies. At the top of the Table 1 are listed the trials with simultaneous blockage with anti-PD-1/PD-L1 and anti-CTLA-4 antibodies, which are expected to be promising regimens in HCC immunotherapy. The high efficacy of the combination therapy was demonstrated in malignant melanoma [5]. Simultaneous inhibition of the B7-CTLA-4 pathway by an anti-CTLA-4 antibody may increase the number of activated CD8+ T cells in lymph nodes, followed by an increase in the number of activated CD8+ T cells infiltrating the tumour tissues, thereby enhancing the antitumor effects. Their combination with molecular targeted agents (e.g., sorafenib or axitinb) also appears promising.

Table 1: Summary of ongoing trials with immune checkpoint inhibitors in HCC.

Clinicaltrial.gov Identifier	Immune checkpoint inhibitor	Trial	Phase	No.	Main endpoint
CTLA-4 + PD-1/PD-L1					
NCT03222076	ipilimumab+ Nivolumab	In patients with resectable of potentially resectable HCC	II	45	Safety, ORR, PFS, conversion to surgery
NCT028221754	Tremelimumab+ Durvalumab	Combined immune checkpoint inhibition in combination with ablative therapies	I/II	90	PFS, Safety
NCT02519348	Tremelimumab+ Durvalumab	Study of Dervalumab with Tremelimumab, durvalumab or Tremelimumab monotherapy in unresectable HCC	II	440	Safety, ORR, OS
PD-1/PD-L1 + other agents					
NCT03071094	Nivolumab	Safety and efficacy of intratumoral Pexa-Vec combined with nivolumab in first line advanced HCC	I/II	30	Safety, ORR, DCR , OS
NCT02423343	Nivolumab	Galunisertib (LY2157299) in combination with nivolumab in advanced refractory solid tumors and in recurrent or refractory HCC	I/II	75	MTD, ORR, DoR, PFS, OS
NCT03419897	BGB-A317	Efficacy, safety, and pharmacokinetics of the anti-PD-1 monoclonal Antibody BGB-A317 in patients with previously treated hepatocellular unresectablecarcinoma	II	228	ORR
NCT03412773	BGB-A317	BGB-A317 versus sorafenib	III	660	PFS, OS
NCT02942329	SHR-1210	Exploratory clinical study of apatinib and SHR-1210 in advanced HCC or gastric cancer	II/II	60	Safety, ORR, DCR, OS
NCT03380130	Nivolumab	Safety and efficacy of nivolumab after SIRT	II	40	Safety, ORR, DCR, OS
NCT01658878	Nivolumab	Efficacy , safety and tolerability of nivolumab in combination with other agents	I/II	620	PFS, OS
NCt02886897	NA	Study of combinations of dendritic cells and cytokine-induced killer cell (D-CIK) immunotherapy and anti-programmed death-1 in refractory solid tumors	I/II	50	PFS, OS
NCT03259867	NA	Combination of TATE and PD-1 inhibitor in liver cancer	II	40	ORR, PFS, OS
NCT02795429	PDR001	Study of INC280 + PDR001	I/II	108	DLT, ORR
NCT03099564	Pembrolizumab	Pembrolizumab + Y90 radioembolization	I	30	Safety, PFS, OS
NCT02658019	Pembrolizumab	Pembrolizumab in advanced HCC	II	35	Safety, PFS, OS
NCT03163992	Pembrolizumab	Pembrolizumab as second-line after failure of sorafenib	II	60	ORR
NCT03062358	Pembrolizumab	Pembrolizumab or placebo given with the best supportive care	III	300	PFS, OS
NCT02988440	PDR001	PDR001 in combination with sorafenib	I	50	MTD
NCT03101488	KN035	Phase I study of KN035 in Chinese subjects with advanced solid tumors & HCC	I	60	DLT, ORR, PFS
NCT03289533	Avelumab	Avelumab in combination with axitinib	I	20	PK, ORR, PFS

In particular, the approach combining an immune checkpoint inhibitor with an existing loco regional therapy for HCC is currently under evaluation. TACE or RFA is expected to enhance the effects of immunotherapy by inducing local inflammation, releasing gneoantigens that activate antigen presentation and immune system activation. The results of the combination therapy with anti-CTLA-4 antibody and loco regional therapy in advanced HCC have recently been published [6]. The NCT01853618 study evaluated the efficacy of adjuvant therapy with tremelimumab (anti-CTLA-4 antibody) after RFA or TACE in several, but not all, HCC nodules, with favourable outcomes, including a partial response rate of 26%, time to tumor progression of 7.4 months, and overall survival of 12.3 months.

The results of trials of the immune checkpoint inhibitor-combined strategies are awaited with high expectations by the medical community.

References

1. El-Serag HB, Mason AC (1999) Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 340: 745-750.

2. Bruix J, Sala M, Llovet JM (2004) Chemoembolization for hepatocellular carcinoma. Gastroenterology 127(5(1)): S179-S188.

3. Yu-Peng H, Zi-Duo L, Pankaj P, Qi Z (2015) Immunotherapy for hepatocellular carcinoma: From basic research to clinical use. World J Hepatol 7(7): 980-992.

4. FDA, US Food and drog Administartion, USA.

5. Larkin J, Chiarion-Sileni V, Gonzalez R, Jean Jacques Grob, C Lance Cowey, et al. (2015) Combined nivolumaband ipilimumab or monotherapy in untreated melanoma 373: 23-34.

6. Duffy AG, Ulahannan SV, Makorova-Rusher O, Wedemeyer H, Pratt D, et al. (2017) Tremelimumabin combination with ablation in patients with advanced hepatocellular carcinoma. J Hepatol 66: 545-551.

DOI: 10.32474/OAJOM.2018.01.000109