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Mini Review



# Nivolumab as a Treatment for Hepatocellular Carcinoma

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## Abstract

Hepatocellular carcinoma is responsible for high mortality and morbidity rates, being the third tumour responsible for cancer-related deaths worldwide. Current treatments for these tumours comprise surgery, chemoembolization, radiation treatments and targeted therapies, such as sorafenib. However, the survival rate of these patients is still very dim, highlighting the need for other therapeutic options, such as immunotherapy.

As with many other tumours, there is an immune deregulation that occurs with hepatocellular carcinoma, resulting in a low expression of T effector cells, also due to the overexpression of immune checkpoints, such as PD-1. As such, PD-1 blockade using drugs like nivolumab is a good alternative to treat patients with liver cancer, with studies showing improved survival and progression free rates.

**Keywords:** Hepatocellular Carcinoma; Immunotherapy; Nivolumab; PD-1; Treatment

**Abbreviations:** CTLA-4: Cytotoxic T Lymphocyte-Associated Antigen-4; CR: Complete response; DCR: Disease Control Rate; HCC: Hepatocellular carcinoma; ICI: Immune Checkpoint Inhibitor; ORR: Objective Response Rate OS: Overall Survival; PD-1: Programmed Cell Death-1; PFS: Progression Free Survival; PR: Partial Response

## Introduction

Hepatocellular Carcinoma is responsible for a high number of cancer related deaths worldwide, earning the third place in worldwide cancer deaths [1,2]. Besides, even with regular examinations and in developed countries only about half the patients have an early diagnosis [1].

At the moment, several treatments are available for patients with HCC, such as surgery (the most effective treatment, but an option for only around one-third of patients), radiofrequency ablation, transarterial chemoembolization, radiation therapy and targeted therapies such as sorafenib and lenavatinib (multikinase inhibitors) or even liver transplantation [1,3,4]. However, even with these treatments, OS and PFS are still very low as most patients have a late diagnosis, with an expected survival of less than one year after diagnosis [3], proving the need for other therapeutic alternatives, such as immunotherapy [1].

In fact, studies have shown the potential benefit of targeting the immune system when it comes to treating patients with HCC, with immune checkpoint blockade being a reliable alternative, using drugs such as nivolumab [3].

In this mini-review we aim to highlight the main features of HCC and the rationale behind the use of ICIs the treatment of patients with these tumours.

### Hepatocellular Carcinoma

Several factors contribute to the development of HCC, namely viral infections such as B and C Hepatitis, alcohol abuse, metabolic syndrome, obesity, non-alcoholic fatty liver disease and autoimmune hepatitis [1,3,5]. Although the majority of cases are reported in lower income countries in Asia, a great number of cases are reported worldwide, possibly related to the life-style usually associated with developed countries [4].

HCC is known to be a tumour with low response rates to conventional chemotherapy, with no single or combined regiment showing survival benefit in HCC [2].

The liver presents with special characteristics regarding immunity, as this organ has dual blood supply which allows the HCC to be immune-tolerated, with a high expression of interleukin-10, increased number of Treg cells and an overexpression of immune checkpoints such as PD-1 and CTLA-4, allowing the tumour to evade the host's immune system and subsequently progress and grow [1,3].

### Nivolumab in the treatment HCC

Nivolumab is a fully humanized PD-1 blocker, allowing T-cell proliferation and immune activation against the tumoural antigens [4]. Checkmate-40 was a trial where patients with HCC previously treated with sorafenib received nivolumab with a response rate lasting 6 months in 91% of patients and 12 months in 51% [1,4].

A study has also shown promising results using a combination of nivolumab+ipilimumab (blocking PD-1 and CTLA-4 at the same time), with a CR in 12% of patients and PR in 22% [1].

The El-Khoueiry trial studied the effect of treating patients with no prior sorafenib treatment with nivolumab, obtaining an ORR of 22.5% and a DCR of 62.5% [3] with an OS of 28.6 months. On the other hand, Checkpoint 459 is a study comparing nivolumab and sorafenib in the first line setting for the treatment of HCC, showing benefit in OS, having 14.7months OS with sorafenib and 16.4 months with nivolumab, although without statistical significance [2,3]. It also showed an IRR of 15% with nivolumab versus 7% with sorafenib [2,5]. Nonetheless, only 1% of patients receiving sorafenib achieved CR, compared to 4% in the nivolumab group [5]. Besides, therapy with checkpoint inhibitors such as nivolumab has a manageable adverse-events profile with the most common being rash, pruritus, diarrhoea, hepatitis and pneumonitis, rarely myocarditis and other serious adverse events [1,2]. These results have granted an accelerated approval for the use of pembrolizumab and nivolumab in the treatment of HCC patients previously treated with sorafenib [2].

However, there was no variability of response when comparing TNM or BCLC staging or even Child-Pugh Score, possibly one of the reasons for not better results regarding nivolumab in HCC treatment, highlighting the need for biomarkers of response to ICIs, such as PD-L1 expression.

## Conclusion

HCC is a tumour with a high mortality rate, being the third cancer worldwide responsible for cancer-related deaths. Furthermore, the current treatments available for patients with HCC, despite improving the OS and PFS, are still not enough to allow for a life expectancy higher than one year in most cases, showcasing the need for alternative therapies such as immunotherapy.

In fact, several studies have shown the potential benefits of ICI in the treatment of patients with HCC, with the use of drugs such as nivolumab and pembrolizumab. Nonetheless, there is still a great need for further studies regarding the use of ICIs and biomarkers of response to these drugs, enabling a better use of immune targeted therapies in HCC.

## Conflict of Interest

There are no conflicts of interest to declare.

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