Hepatocellular carcinoma (HCC) is the second cause of cancer-related death worldwide and its incidence is steadily increasing. HCC primarily develops from cirrhosis, and most patients are infected with hepatitis C or B virus. Non-viral HCC etiologies, such as diabetes mellitus and non-alcoholic steatohepatitis (NASH), are growing in frequency particularly in Western European patients. Unfortunately, more than 750,000 cases are diagnosed each year and the majority of them are at advanced stages when curative treatments are very difficult to apply. For advanced HCC, the first-line systemic therapy option is the multikinase inhibitor sorafenib, which offers an increase in overall survival from 7.9 months to 10.7 months when compared to placebo. Although a large majority of patients progress on sorafenib, treatment with regorafenib in second line, a similar molecule in terms of mechanisms of antitumoral activity and side effects, improved overall survival by 2.8 months vs. placebo. Therefore, there is an urgent need for more effective options for patients with advanced HCC.

Liver immunotolerance

It is well known that cancer is a complex and multifactorial disease; tumor cells have the ability to release a number of immunosuppressive factors, which can prevent the recognition and destruction of tumor cells by the immune system. The liver, being a site of immune activity, plays a critical role in the development and progression of HCC. Studies have shown that the liver has a unique microenvironment that can both help and hinder the antitumor immune response. For example, the liver can produce regulatory T cells (Tregs) that can suppress immune responses, while also being a site of activation of innate immune cells such as natural killer cells and dendritic cells.

Furthermore, the liver has a unique circulatory system that allows for the rapid delivery of immunosuppressive factors from the systemic circulation to the tumor microenvironment. This can lead to a situation where the tumor is protected from immune attack, even in the presence of an active immune response elsewhere in the body.

However, recent advances in immunotherapy have shown that the liver can also be a site of tumor regression. Immunotherapy, such as checkpoint inhibitors, has shown promise in the treatment of HCC, and recent studies have shown that the liver can be a site of regression with checkpoint inhibitors. This suggests that the liver has the potential to be a site of immune attack, and that further studies are needed to better understand the role of the liver in the development and progression of HCC.

In conclusion, the liver is a unique site of both immune suppression and potential immune attack in the development of HCC. Further studies are needed to better understand the role of the liver in the development and progression of HCC, and to develop effective strategies for immunotherapy in this setting.
of factors that can assist their capacity to grow and metastasize. One of the most important characteristics of tumors is their capacity to evade immune surveillance. Preclinical and clinical data demonstrated that the intra-tumoral microenvironment is highly immunosuppressive and there is a poor effector T cell response in advanced HCC. Independently of the causative disease, HCC can be considered as an inflammatory tumor composed by different types of immune cells that tilt the balance toward a state of immunotolerance. This immunosuppressive microenvironment is characterized, at least in part, by the presence of CD4+ FoxP3+ T cells (Tregs), type 2 macrophages, myeloid-derived suppressor cells, tumor associated fibroblasts, Kupffer cells, just to mention a few. It has been previously reported that tumor-infiltrating lymphocytes correlate with improved survival in patients with HCC. Thus, it is reasonable to consider immunotherapy as a rational therapeutic tool for patients with advanced or progressed HCC. The main goal of the majority of immunotherapy approaches is to generate a potent specific cytotoxic T cell response against cancer cells. The list of strategies applied so far include tumor vaccines, adoptive T cell therapy (including CAR-T cells), immune-gene therapy with oncolytic vectors, dendritic cells-based vaccines and, more recently, the use of immunostimulatory monoclonal antibodies, particularly the immune checkpoint inhibitors. Checkpoint blockade has become a major focus in the immune-based therapy of HCC. The main concept involves inhibition of regulatory cell surface molecules, which normally inhibit T-cell activation.

**Immune checkpoint antibody therapy for HCC**

Sangro et al demonstrated in a pilot study that the Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) inhibitor tremelimumab has promising antitumoral activity in patients with advanced HCC with hepatitis C virus infection. Twenty patients were treated with tremelimumab resulting in 17.6% of partial response and an overall survival of 8.2 months. More recently, a phase 1/2 dose escalation and expansion trial (CheckMate 040) evaluated nivolumab in sorafenib-naïve as well as in sorafenib-experienced HCC. Nivolumab is a fully human (IgG4) monoclonal antibody

<table>
<thead>
<tr>
<th>Monoclonal antibody/target</th>
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<tbody>
<tr>
<td>Nivolumab/anti-PD-1</td>
<td>Randomized open-label phase III; nivolumab vs. sorafenib</td>
<td>Not available</td>
<td>NCT02576509</td>
</tr>
<tr>
<td>Nivolumab/anti-PD-1</td>
<td>Phase 1/2 dose escalation and expansion trial. Nivolumab in sorafenib-naive and sorafenib-experienced patients</td>
<td>Objective tumor response of 20%, and stable disease of 45% in the expansion cohort.</td>
<td>NCT01658878 - Ref. 15</td>
</tr>
<tr>
<td>Tremelimumab/anti-CTLA4</td>
<td>Phase II study; HCV infected patients</td>
<td>17.6% of partial response, and an overall survival of 8.2 months</td>
<td>NCT01008358 - Ref. 14</td>
</tr>
<tr>
<td>Pembrolizumab/anti-PD-1</td>
<td>Prospective single arm open label</td>
<td>Not available</td>
<td>NCT02702414</td>
</tr>
<tr>
<td>Pembrolizumab/anti-PD-1</td>
<td>Prospective randomized double-blind phase III; pembrolizumab + best supportive care vs. placebo + best supportive care</td>
<td>Not available</td>
<td>NCT02702401</td>
</tr>
<tr>
<td>Durvalumab/anti-PD-1-L</td>
<td>Phase I multiarm dose expansion study Interventional randomized</td>
<td>0% objective tumor response; 10% grade 3 adverse events.</td>
<td>NCT01693562 - Ref. 19</td>
</tr>
<tr>
<td>Durvalumab/antiPD-1-L + tremelimumab/anti-CTLA4</td>
<td>Phase II study in subjects with unresectable HCC</td>
<td>Not available</td>
<td>NCT02519348</td>
</tr>
<tr>
<td>Tremelimumab + chemoembolization or ablation</td>
<td>Interventional non-randomized Phase I study</td>
<td>Not available</td>
<td>NCT01853618</td>
</tr>
</tbody>
</table>
inhibitor of the programmed death-1 (PD-1) receptor that restores T-cell–mediated antitumor activity.\textsuperscript{15} Nivolumab has demonstrated clinical benefit in melanoma, refractory non-small cell lung cancer, advanced renal cell carcinoma, Hodgkin lymphoma, squamous cell carcinoma of the head and neck, and urothelial carcinoma.\textsuperscript{16} In the CheckMate 040 study, 262 patients were enrolled and the primary end point was safety and tolerability (escalation phase) and overall response rate (expansion phase). As a result, in sorafenib-experienced patients with or without chronic viral hepatitis, nivolumab demonstrated a long-term survival and durable objective responses; in addition, safety profiles of nivolumab were similar to what has been observed in other tumor types; importantly, hepatic safety events were also manageable. Of note, clinical responses occurred irrespective of PD-L1 expression on cancer cells. A phase 3 study evaluating nivolumab in systemic treatment–naive patients with advanced HCC is being carried out (CheckMate 459, ClinicalTrials.gov identifier NCT02576509) and will be of paramount importance if the study confirms the results obtained with nivolumab in phase 1/2 trial.

These promising results open the possibility for combinations using checkpoint inhibitors such as tremelimumab with other strategies, for example loco-regional treatments (local ablation or trans-arterial chemoembolization) which release tumor antigens into the bloodstream. Duffy et al reported promising results in terms of overall survival and objective responses; interestingly, patients showing increased intratumoral levels of CD8+ T cells, reached better clinical outcome.\textsuperscript{17}

Nivolumab showed similar immune-related adverse events in HCC patients in comparison with other types of tumors; no serious liver dysfunction or autoimmune disease was observed.\textsuperscript{17} El-Khoueiry et al reported that in the dose-escalation phase of the CheckMate040 trial only one of 48 patients who received nivolumab at the dose of 3 mg/kg discontinued therapy due to elevated liver transaminases. One patient showed grade 4 toxicity because of increased lipase, and the only grade 3 events were elevated AST levels in 5 patients and elevated ALT levels in 4 more patients.\textsuperscript{18} In the dose expansion phase (n = 214) HCC patients were treated with 3 mg/kg; in this phase, 40 (19%) patients presented grade 3/4 treatment-related adverse events (Table 1).

Recently, Rammohan et al reported the first case of metastatic HCC following liver transplantation that responded to the PD-1 inhibitor pembrolizumab, after the failure of sorafenib therapy.\textsuperscript{19} The patient showed complete radiological response and remains well with no evidence of tumor recurrence or organ rejection.

In conclusion, the liver constitutes a unique immunological microenvironment, with multiple immunotolerant mechanisms that favor HCC development. Re-establishing anti-tumor immunity seems to be feasible and the results with checkpoint inhibitors such as nivolumab are promising; however, confirmation of the efficacy of nivolumab in the phase 3 clinical trial is pending. It is also important to identify predictive immunological biomarkers to help hepatologists in therapeutic decision-making. Efficacy may be further increased by combining checkpoint inhibitors (e.g. nivolumab and ipilimumab), though with increased toxicity, or by applying loco-regional treatments.

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**Conflicts of interest:** None to declare

**References**


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**LA TAPA**

**Daniela Kantor**, Cañadón, 2017

Acrílico sobre tela. 31.5 × 49.5 cm


Fuentes: [www.danielakantor.com](http://www.danielakantor.com); [www.kantorconk.blogspot.com](http://www.kantorconk.blogspot.com); [www.danikantor.portfoliobox.net](http://www.danikantor.portfoliobox.net)