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Review article

# Immunotherapy for hepatocellular carcinoma: A review of potential new drugs based on ongoing clinical studies as of 2019

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ABSTRACT

In the latest years, antineoplastic immunotherapy revolutionised the therapeutic landscape in oncology. First shown to be effective in melanoma and non-small cell lung carcinoma, immune checkpoint inhibitors are now being tested for the treatment of hepatocellular carcinoma (HCC). Preliminary results have been particularly promising. As a consequence, an increasing number of clinical trials are underway. The role of the immune system in carcinogenesis (with particular reference to tumour escape immune mechanisms), as well as the current immunotherapy trials for HCC in its different clinical scenarios, are the subject of this review. In particular, we aim to provide fresh updates about these novel therapeutic agents which promise to shape the future therapeutic scenario of HCC.



## 1. Introduction

Hepatocellular carcinoma (HCC) is among the most deadly cancers worldwide, despite surveillance programs and many available treatments, including liver transplantation, surgical resection, percutaneous and endovascular procedures, as well as pharmacological treatments [1]. The majority of HCCs occur in patients whose liver suffered some degree of inflammation. The main risk factors for HCC include, in fact, HBV, HCV, obesity, excessive alcohol consumption and metabolic diseases, all of which contribute to a condition of chronic hepatitis, eventually leading to fibrosis and cirrhosis, held as pre-neoplastic situations. Therefore this tumor appears very intriguing to try to understand the relationship between the immune system, inflammation and cancer development [2,3]. It has been hypothesised that an altered liver microenvironment contributes to produce HCC by reprogramming the inflammatory environment [4]. Thus, an in-depth look at liver immunology in HCC would improve our understanding of the immunological mechanisms that occur during hepatocarcinogenesis and could lead to new and improved treatment strategies for this deadly disease.

This review concisely illustrates the mechanism of tumor immune escape and presents a complete standpoint of immunotherapy drugs under current clinical investigation for HCC as of 2019.

During carcinogenesis, the transformation of normal cells into malignant cells is associated with the expression of tumour-associated antigens (TAAs), that will be presented on the cell surface by a group of proteins known as the major histocompatibility complex (MHC) [5] (Fig. 1A). These antigens will also be retrieved and presented by antigen-presenting cells (APCs).

The APCs migrate to lymph nodes where they display TAAs to the T-cell receptors (TCR) located on the surface of immature T-cells (Fig. 1B). However, the simple binding of TAAs with TCRs is insufficient to activate immature T-cells, but rather a co-stimulation is necessary. In particular, APCs and immature T-cells co-stimulation require the binding of B7 proteins (CD80/B7-1 and CD86/B7-2), which are hosted on antigen-presenting cells, to CD28, which instead is presented by immature T-cells. This binding and the consequent co-stimulation leads to the activation of such T-cells, which become CD8+T-cells (trigger phase) (Fig. 1C). The activated T-cells subsequently migrate from the lymphnodes to the lymphatic vessels and then to the bloodstream until reaching the tumour microenvironment. In the tumor microenviroment CD8+T-cells recognise the TAAs presented by the MHC on the cancer cells and attack them (effector phase) (Fig. 1D), eventually eliminating tumor cells [5–7].

This process is obviously finely modulated at a local and general level. The most relevant steps for such fine modulation discovered

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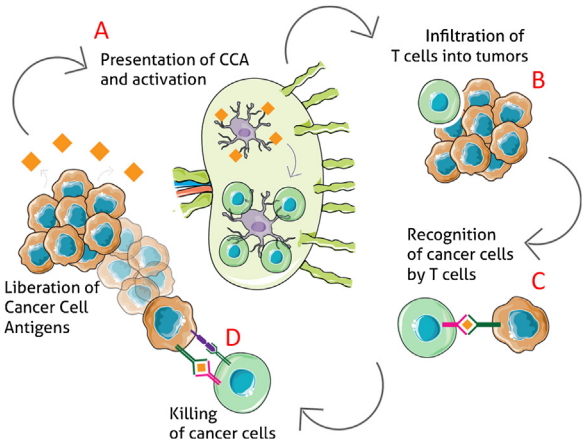


**Fig. 1.** Interactions between cancer cell antigens (CCA) and the immune system. After their release, CCA reach the antigen presenting cells (A). The identification of CCA by the antigen presenting cells leads to a priming of the T-cells and their eventual migration into the tumor (B). This phenomenon is normally followed by a T-cell-mediated recognition (C) and killing (D) of the cancer cells.

so far are those involving the immune checkpoint inhibitors, consisting in molecules bound to the outer membrane of the immune system cells. The most largely studied immune checkpoints are cytotoxic T lymphocytic protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1).

CTLA-4 is essential for the activation of CD4+T-cells and the triggering phase of the immune response. Its main ligands are CD80 and CD86 in activated T-cells. The binding of CTLA-4 with these ligands prevent their interaction with CD 28, finally resulting in a decrease in T-cell activation by antigen presentation (Fig. 2A).

CTLA-4 is also constitutively expressed by regulatory T-cells (Tregs) which are CD4+T-cells characterised by the expression of CD25, CTLA-4, CD62L and FoxP3 molecules [8]. Once activated, Tregs inhibit the immune response through IL-2 or produce immunosuppressive factors such as TGF-b, IL-10 or adenosine [9]. They also need CTLA-4 to be able to exert their suppressive activity. In addition to its role in modulating the trigger phase through a block of the CD28, CD80 and CD86 interactions, CTLA-4 also promotes immunosuppression within the tumour by inducing Treg activity and differentiation.

PD-L1 and PD-L2 are the PD-1 ligands (Fig. 2B). PD-L1 is expressed on immune system cells (antigen-presenting cells and MDSCs), whereas PDL-2 is generally expressed in the hemopoietic compartment. Several cytokines, in particular, IFN-gamma, regulate PD-L1 [10]. After binding to its ligands, PD-1 inhibits CD8+T-cell activation by blocking TCR signalling and also inhibits the activation and proliferation of CD4+ by increasing IL-10 secretion. Cancer cells express PD-L1 and PD-L2, using this mechanism to escape immunosurveillance. In fact, IFN-gamma produced by TAA-specific T-cells in a situation of chronic antigen exposure, induces PD-1 expression in T-reactive lymphocytes and upregulates PD-L1 in APCs and tumour cells. The PD-1–PD-L1 graft then blocks TCR signalling and inhibits the proliferation and secretion of cytotoxic T-cell mediators in a process known as T-cell exhaustion. Altogether therefore the CTL4 and PD-1/PD-L1 pathways appear relevant in achieving (tumor) or blocking (therapy) the cancer immune escape.

Accordingly, the possibility to target the checkpoint inhibitors pathway has been a radical innovation in the field of the systemic treatments for HCC in recent years [11]. The inhibition of the most critical immune checkpoint can be reached by blocking CTLA-4, PD-1 or its ligand PD-L1. Ipilimumab and tremelimumab are the most longly tested CTLA-4 inhibitors. Nivolumab, pembrolizumab, spartalizumab, camrelizumab, and tislelizumab have shown a strong PD-1 inhibitory activity. PD-L1 blockers have been developed more recently, currently including durvalumab, avelumab and atezolizumab.

## 2. Concluded trials

Historically, tremelimumab was the first checkpoint inhibitor tested explicitly in HCC patients. In an investigator-initiated Phase II open-label, multicenter clinical trial, Sangro et al recruited 21 patients with HCV-related HCC [12]. Most patients (57.1%) had an advanced stage disease and were naïve to sorafenib (76.2%). Patients were treated until tumour progression or unacceptable toxicity. Objective response and disease control rate were 17.6 and 76.4%, respectively. Median time to progression (TTP) was 6.48 months (95% CI: 3.95–9.14). No toxicities requiring systemic steroid treatment were registered.

These favourable results were followed shortly after by the announcement of a multicohort Phase 1b/2 trial of nivolumab alone or combined with ipilimumab in HCC (Checkmate-040, NCT01658878). The results from the dose escalation and expansion cohorts displayed an unprecedented overall response rate (ORR) for systemic therapy in HCC [13]. Across dose escalation and expansion

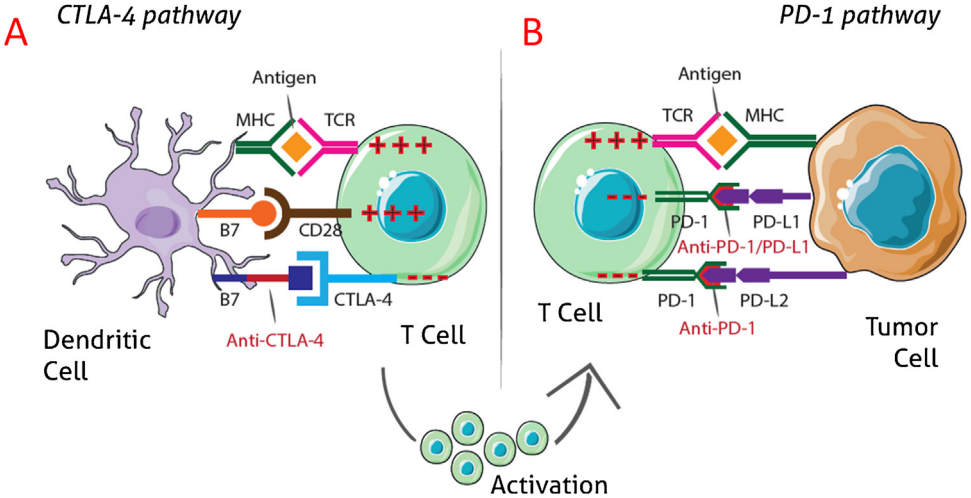


**Fig. 2.** Roles of PD-1 and CTLA-4 checkpoints in the immune response to cancer cells. While the CTLA-4 checkpoint is mainly involved the dendritic cells-mediated priming of T-lymphocytes, the PD-1 pathway is primarly involved in the in the direct interaction between T-lymphocytes and tumor cells.

phases (262 patients), grade 3/4 treatment-related adverse events occurred in 20%. The ORR was 20% (95% CI: 15–26) in 214 patients treated in the dose expansion phase with a median duration of response of 9.9 months and a disease control rate of 64% (95% CI: 58–71).

Similar therapeutic efficacy was observed in another open-label nonrandomized Phase 2 trial of pembrolizumab in patients who progressed or were intolerant to sorafenib (Keynote-224) [14]. This multicentre study enrolled 104 patients who received 200 mg pembrolizumab intravenously every three weeks until disease progression or unacceptable toxicity. The ORR was 17%, and the disease control rate was 61%. Grade 3 treatment-related events were reported in 24% of patients, and the most common were increased aminotransferases and fatigue. A single grade 4 (hyperbilirubinemia) and a grade 5 treatment-related event (ulcerative oesophagitis) occurred. Of note, immune-related hepatitis occurred in three patients but was easily managed. Most recently, the results of nivolumab in the dedicated Cohort 5 of the Checkmate-040 study were revealed. In 49 treated patients (25 sorafenib-naïve and 24 sorafenib experienced), the overall response rate was 10.2% with a disease control rate of 55.1%, a median overall survival of 7.6 months, and a safety profile comparable with that of Child-Pugh A patients [15].

Based on the results of the Checkmate-040 and Keynote-224 trials, the United States Food and Drug Administration (FDA) granted on accelerated approval to nivolumab in September 2017 and a priority review to pembrolizumab for the second line systemic treatment of HCC in July 2018. In July 2018, the FDA also granted a breakthrough therapy designation for HCC to the combination atezolizumab plus bevacizumab following a multicenter Phase 1b trial in which patients were randomised in 5 different treatment arms [16]. Amongst the 23 patients assigned to the combination arm, 14 (61%) had an objective response to treatment. Other regulatory agencies, such as the European Medicine Agency (EMA), have been more cautious so far and will wait for more evidence before approving these molecules for HCC, even in a non definitive modality. This call for caution has been shown to be justified most recently, as the Phase 3 Keynote-240 trial did not confirm the result of the previous Phase 2 trials, failing to demonstrate the benefit of pembrolizumab over placebo in the second line setting [17]. In the final analysis of the study, there was an improvement in OS for patients treated with pembrolizumab compared to placebo, however these results did not meet statistical significance per the pre-specified 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 statistical significance (HR = 0.78 [95% CI, 0.61–0.99]; p = 0.0209) [17].

## 3. Immune-related adverse events and overall safety of immune checkpoint inhibitors immune-related adverse events and overall safety of immune checkpoint inhibitors

Inhibition of the physiological immune checkpoints can be associated with immune-related adverse events, both organ and non-organ specific. Virtually, any tissue and organ can be involved [18,19]. In the seminal clinical trials of nivolumab, the skin, gut, thyroid, adrenal glands, lung and liver were the most frequent target of immune-related adverse events [13]. However, nivolumab was overall well tolerated and associated with a very low rate of grade ≥3 events, including diarrhea, pemphigoid-like skin reaction, adrenal failure, and hepatitis [13]. Ipilimumab alone or in combination with nivolumab, was instead associated with a relatively higher rate of aminotransferase elevation (45% and 25% for aspartate and alanine aminotransferase, respectively) [12,20]. These immune-related adverse events were generally easily managed with a schedule delay and corticosteroids in the most severe and/or unresponsive cases. Only a very limited number of fatal outcomes due to immune-related pneumonitis [21] and miocarditis [22] have been described so far in the treatment of different cancers. Until now, a single case of a treatment-related fatal event was reported in HCC trials of immune checkpoint inhibitors (ulcerative oesophagitis) [14].

Despite this reassuring safety profile, the use of immune checkpoint inhibitors in the fragile setting of cirrhotic patients was initially accompanied with a justifiable dose of safety concerns. In particular, the risk of immune-mediated hepatitis and the possible side effects deriving from the use of corticosteroids in cirrhotic patients were seen as critical elements. In the seminal study of tremelimumab in HCC by Sangro et al. [12], almost half of patients had a aminotransferase increase after treatment. These alterations were transient, never associated with liver function impairment, and did not require prescription of corticosteroids. In the Checkmate-040 study, an increase in aminotrasferase levels was found in 22–30% of the patients receiving nivolumab. A similar rate was also described in the Keynote-224 study of pembrolizumab [14]. These data have been also confirmed in the preliminary analysis of other Phases 1–2 trials investigating different agents, including durvalumab, camrelizumab, and atezolizumab [23–26]. The need for corticosteroids to treat immune related adverse events has been relatively low (maximum 6%) so far [26]. Overall, the safety profile of immune checkpoint inhibitors in HCC patients was consistent with that reported in previous studies for melanoma and lung cancer, suggesting that these patients do not suffer an increased risk of liver immune-related adverse events. These comforting data found further confirmation in the recently presented data of nivolumab in Child–Pugh B patients. In this cohort of particularly frail patients, treatment related hepatic adverse events were described in only 4 out of 49 patients, leading to treatment discontinuation in 2 patients [15].

In conclusion, immune checkpoint inhibitors seem to be generally well tolerated even in patients with HCC and underlying liver cirrhosis. To date, however, caution is still needed since these agents have been tested only in the very recent period, but are known to potentially produce also delayed toxicities. More evidence deriving from the long term follow up of responder patients will help elucidate this specific point.

## 4. Ongoing trials

Unsurprisingly, the interest toward immune checkpoint inhibitors is on the rise in Oncology overall and HCC is no exception. Currently, more than 60 studies of these molecules have been registered in Clinicaltrials.gov. The design of these studies is varied. For instance, checkpoint inhibitors are being investigated as single agents or in combination with other in the advanced as well as in the adjuvant and neoadjuvant setting. In the next paragraphs, we will summarise these currently ongoing studies.

### *4.1. Advanced setting — monotherapy or combination of two immune checkpoint inhibitors*

By the end of 2018, to the best of our knowledge, five Phase 3 randomised clinical trials (RCTs) are exploring this setting (Table 1). In the second line scenario, the Keynote-240 has been recently announced to have failed its primary endpoint of increased OS over placebo in a Western setting. The Keynote-394 trial, however is still ongoing and trying to confirm the superiority of pembrolizumab over placebo in Eastern populations.

The competition is tougher in the first line scenario, where nivolumab, tislelizumab and the combination tremeli-

**Table 1**
Ongoing clinical trials exploring immune checkpoint inhibitors as treatment for advanced hepatocellular carcinoma.

| NCT | Phase | Study drug(s) | Line | Primary endpoint | Estimated end of trial |
|---|---|---|---|---|---|
| NCT02576509 | 3 | Nivolumab vs sorafenib | 1 | OS | Dec 2019 |
| NCT03298451 | 3 | Tremelimumab(+durvalumab) vs sorafenib | 1 | OS | Mar 2021 |
| NCT03062358 | 3 | Pembrolizumab vs placebo[a] | 2 | OS | Apr 2021 |
| NCT02702401 | 3 | Pembrolizumab vs placebo | 2 | OS, PFS | Feb 2019 |
| NCT03412773 | 3 | Tislelizumab vs sorafenib | 1 | OS | May 2022 |
| NCT02519348 | 2 | Tremelimumab (+durvalumab) | 2 | AEs, DLT | Dec 2019 |
| NCT02658019 | 2 | Pembrolizumab | >2 | DCR, AEs | Apr 2020 |
| NCT02702414 | 2 | Pembrolizumab | 1–2 | ORR | May 2020 |
| NCT03163992 | 2 | Pembrolizumab | 2 | ORR | Dec 2019 |
| NCT03389126 | 2 | Avelumab | 2+ | ORR | Mar2020 |
| NCT03419897 | 2 | Tislelizumab | 2+ | ORR | Sep 2021 |
| NCT01658878[b] | 1B/2 | Nivolumab vs sorafenib | 1 | ORR | Jul 2019 |
| NCT01658878[b] | 1B/2 | Nivolumab + ipilimumab | 2+ | ORR | Jul 2019 |
| NCT02423343 | 1B/2 | Nivolumab + galunisertib | 2 | MTD, AEs | Dec 2019 |
| NCT02828124 | 1/2 | Nivolumab | Any | AE | Oct 2020 |
| NCT02940496 | 1/2 | Pembrolizumab | 2 | Biomarker | Dec 2019 |

NCT: number of clinical trial (Clinicaltrials.gov); OS: overall survival; PFS: progression free survival; AEs: adverse events; DLT: dose limiting toxicities; DCS: disease control rate; MTD: maximum tolerated dose.
[a] Study performed in Asian population only.
[b] Multi-cohort study.

mumab/durvalumab are being tested versus sorafenib in their respective Phase 3 RCTs. The results of these trials are expected no earlier than mid 2019. In the meantime, preliminary results of the trials of camrelizumab and, durvalumab in monotherapy or in combination with tremelimumab have been recently presented in abstract form at relevant oncology meetings and seem to confirm an objective response rate of 15–20% with a good safety profile [23–26]. Other interesting preliminary data might come from some of the still ongoing Phase 2 RCTs. In particular, the results of the Cohort 3 (nivolumab vs sorafenib) and of the Cohort 4 (nivolumab + ipilimumab vs placebo) of the already mentioned Checkmate-040 study are expected in late 2019.

### *4.2. Advanced setting — combination of immune checkpoint inhibitors with other agents*

The possibility to combine the therapeutic effects of drugs with different mechanism of action has always been intriguing. The simultaneous blockade of many neoplastic crossroads offers, in fact, a higher probability of obtaining a disease control. In the specific case of HCC, the combination of anti-VEGFR agents and immune checkpoint inhibitors could also have synergistic effects given the fact that molecular target agents could collectively block the signalling from various growth factors and affect immune effectors and the vasculature [27,28]. As a consequence, most clinical trials of combined therapy are exploring immunotherapy paired with oral tyrosine inhibitors (mainly sorafenib, lenvatinib, regorafenib, cabozantinib, vorolanib, and axitinib) or intravenous anti-VEGFR monoclonal antibodies (bevacizumab, ramucirumab) (Table 2). However a more potent antitumor effect is not necessarily associated with longer survival in the specific setting of HCC, since this tumor most commonly arises in a background of advanced liver disease, whose worsening might be as lethal as the tumor progression. This risk was shown by the failed sunitib vs sorafenib Phase 3 trial [29] where the potency of the antitumoral effect was undermined by the occurrence of severe cirrhosis related adverse events at the choosen dosage.

In the frontline setting, a Phase 3 RCT of atezolizumab plus bevacizumab vs sorafenib is currently ongoing to confirm the results of the Phase 1b trial which led the FDA to grant a breakthrough therapy designation to this combination. Interesting data came form the Phase 1b trial of pembrolizumab plus lenvatinib. Amongst the 18 participants of the study, almost half (46%) had a partial response in absence of new safety concerns signals [30]. Other interesting information may come from the Cohort 6 of the Checkmate-040 study, in which the combination nivolumab (with or without ipilimumab) plus cabozantinib is being tested both in a mixed population of sorafenib-naïve and pretreated patients.

Combination strategies of the immune checkpoint inhibitors are not limited to the anti-VEGFR drugs. In particular, different trials are also evaluating combinations with transforming growth factor-beta oral inhibitors (galunisertib), c-MET oral inhibitors (capmatinib), anti-phosphatidylserine antibodies (bavituxumab), and heat shock protein 90 inhibitors (XL-888). Of particular interest, some trials are exploring the mechanisms that may lead to the tumour resistance (and eventual progressions) to the currently known checkpoint inhibitors. The main aim is to identify other modulators of the immune system which may help in overcoming this resistance. For instance, INCAGN01876 is a modulator of glucocorticoid-induced tumour necrosis factor receptor which is being tested in combination with nivolumab plus ipilimumab and pembrolizumab in two distinct Phase 1b/2 trials. Also, the C-C chemokine receptor 4 (CCR4) inhibitor mogalizumab is claimed to enhance the antibody-dependenT-cell-mediated cytotoxicity and is currently being tested in combination with nivolumab. Similarly, EPACADOSTAT and INCAGN01949 are two drugs targeting indoleamine 2,3-dioxygenase and the T-cell costimulatory molecule CD134 which are being tested in combination with the current checkpoint inhibitors. Finally, the combination of immunotherapy and anticancer vaccines (Pexavec, T-VEC and p53MVA) is also being explored.

Whether such combination therapies will produce a higher rate of and/or longer lasting antitumoral effect and will translate into prolonged survival for HCC patients will require some years to be demonstrated.

### *4.3. Adjuvant and neoadjuvant setting*

To prevent, or at least delay recurrence after achieving a complete response of the primary HCC with resection or locoregional therapy has always been a target of primary importance. In fact patients may suffer spread of the primary tumor or occurrence of a de novo tumor due to the underlying cirrhosis. Unfortunately, no drugs have been found able to achieve this goal in HCC so far. In particular, the STORM trial did not show any advantage in patients treated with sorafenib compared to placebo in terms of

**Table 2**
Ongoing clinical trials exploring immune checkpoint inhibitors in combination with other agents as treatment for advanced hepatocellular carcinoma.

| NCT | Phase | Study drug(s) | Line | Primary endpoint | Estimated end of trial |
|---|---|---|---|---|---|
| NCT03434379 | 3 | Atezolizumab + bevacizumab vs sorafenib | 1 | OS, ORR | JUN 2022 |
| NCT03439891 | 2 | Nivolumab + sorafenib | 1 | MTD, ORR | Dec 2020 |
| NCT03519997 | 2 | Pembrolizumab + bavituximab | 1 | ORR | Apr 2021 |
| NCT01658878[a] | 1B/2 | Nivolumab (+ipilimumab) + cabozantinib | Any | ORR | Jul 2019 |
| NCT02423343 | 1B/2 | Nivolumab + galunisertib | 2 | MTD, AEs | Dec 2019 |
| NCT03126110 | 1B/2 | Nivolumab + ipilimumab + INCAGN01876 | 3 | AE, ORR | Mar 2020 |
| NCT02509507 | 1B/2 | Pembrolizumab + T-VEC | Any | DLT,ORR | Mar 2023 |
| NCT03211416 | 1B/2 | Pembrolizumab + sorafenib | 1 | ORR | Oct 2019 |
| NCT03418922 | 1B | Nivolumab + lenvatinib | 1 | AEs, DLT | Jun 2020 |
| NCT03511222 | 1B | Pembrolizumab + vorolanib | 2 | RP2D | Feb 2022 |
| NCT03289533 | 1B | Avelumab + axitinib | 1 | AEs | Aug 2020 |
| NCT02705105 | 1A/2 | Nivolumab + mogamulizumab | 3 | MTD, DLT | Oct 2018 |
| NCT02859324 | 1A/2 | Nivolumab + avadomide | 1–3 | DLT, AEs, ORR | Mar 2020 |
| NCT03241173 | 1A/2 | Nivolumab + ipilimumab + INCAGN01949 | 2[b] | AEs, ORR | Nov 2021 |
| NCT02178722 | 1A/2 | Pembrolizumab + epacadostat | 2–3 | DLT, ORR | Feb 2020 |
| NCT03277352 | 1A/2 | Pembrolizumab + INCAGN01876 | Any | AEs, ORR | Feb 2020 |
| NCT03071094 | 1–2A | Nivolumab + pexavec | 1 | AEs, ORR | Oct 2019 |
| NCT03475953 | 1–2 | Avelumab + regorafenib | 2+ | RP2D, ORR | Apr 2021 |
| NCT02795429 | 1–2 | Spartalizumab (+capmatinib) | 1 | DLT, ORR | Dec 2019 |
| NCT03382886 | 1 | Nivolumab + bevacizumab | 2–3 | MTD, | Mar 2023 |
| NCT03006926 | 1 | Pembrolizumab + lenvatinib | 1/2 | AEs, DLT, ORR | Dec 2020 |
| NCT03347292 | 1 | Pembrolizumab + regorafenib | 1 | AEs, DLT | Oct 2020 |
| NCT03095781 | 1 | Pembrolizumab + XL888 | 2 | RP2D | Jun 2023 |
| NCT02432963 | 1 | Pembrolizumab + p53MVA | Any | AEs | Feb 2019 |

NCT: number of clinical trial (Clinicaltrials.gov); OS: overall survival; ORR: overall response rate; MTD: maximum tolerated dose; AEs: adverse events; DLT: dose limiting toxicities; RP2D: recommended dose for Phase 2.
[a] Multi-cohort study.
[b] Only after failure of previous treatment with immune checkpoint inhibitors.

**Table 3**
Ongoing clinical trials exploring immune checkpoint inhibitors in the adjuvant and neoadjuvant setting.

| NCT | Phase | Study drugs | Setting | Primary endpoint | Estimated end of trial |
|---|---|---|---|---|---|
| NCT03383458 | 3 | Nivolumab vs placebo | ADJ | RFS | Jun 2025 |
| NCT03222076 | 2 | Nivolumab vs nivolumab + ipilimumab | NADJ | AEs | Sep 2023 |
| NCT03510871 | 2 | Nivolumab + ipilimumab | NADJ | ORR[a] | Dec 2012 |
| NCT03337841 | 2 | Pembrolizumab | NADJ | 1Y-RFS | Oct 2020 |
| NCT03299946 | 1 | Nivolumab + cabozantinib | NADJ | AE, FEASABILITY | Mar 2022 |

NCT: number of clinical trial (Clinicaltrials.gov); ADJ: adjuavant; RFS: recurrence free survival; NADJ: neoadjuvant; AEs: adverse events; 1Y-RFS: 1-year recurrence free survival.
[a] Expressed as rate of patients achieving a target lesion shrinkage >10%.

recurrence-free survival [31]. Moreover, the low rate of objective response of sorafenib and other tyrosine kinase made these drugs particularly unsuitable in the neoadjuvant setting. Immune checkpoint inhibitors may theoretically have the ability to enhance the immune response against residual tumour cells after liver resection. Furthermore, their relatively high rate of objective response, particularly when given in combination, could also be helpful in reducing tumour burden within the criteria of surgical resectability in some patients with intermediate or even advanced disease. The validity of the first point has been confirmed by the results of a Phase 1 trial of tremelimumab in combination with local ablation procedures. In this study, 32 patients were given tremelimumab at two different dose levels, followed by subtotal radiofrequency ablation or chemoablation at Day 36. Nineteen patients were evaluable for response. Five of them achieved a complete radiological response. No dose limiting toxicities were found. Even more interestingly, tumor biopsies performed 6 weeks after tremelimumab revealed an accumulation of intratumoral CD8 + T cells. The Authors therefore concluded that the re-activated immune system could potentially recognize and kill the cancer left behind by a subtotal ablation [32].

Currently, nivolumab is being investigated versus placebo in the adjuvant setting following curative treatments (resection or local ablation) in Phase 3 CHECKMATE-9DX trial (Table 3). The role of nivolumab alone or in combination with either ipilimumab or cabozantinib respectively is also under investigation as a presurgical treatment. Similarly, a trial of pembrolizumab is also ongoing in the neoadjuvant setting.

### *4.4. Combination of immune checkpoint inhibitors with local treatments*

In rare circumstances, localised treatment of a metastatic tumour can lead concurrently to a shrinkage of both the cancer lesion target (or within scope) of therapy and of other untreated lesions localized elsewhere in the body. Described for the first time after local radiotherapy treatment, this phenomenon has since been named “abscopal effect”. It has been postulated that the liberation of tumour-associated antigens after the local destruction lead to the priming of immune cells. Theoretically, immune checkpoint inhibitors may enhance this phenomenon. As mentioned earlier, the CHECKMATE-9DX trial will evaluate the putative benefit of nivolumab not only after liver resection but also after local ablation. Phase 2 trials are also evaluating tremelimumab in a similar setting (Table 4). Similarly to the local ablation treatments, even transarterial treatments may promote the liberation of tumour-associated antigens. Combined treatments of transarterial chemoembolization plus nivolumab or pembrolizumab are ongoing. Transarterial radioembolization promotes radiation-induced tumour damage which is partially similar to that induced by stereotactic body radiation therapy. Both techniques are also expected to be associated with various immune checkpoint inhibitors in different trials.

**Table 4**
Ongoing clinical trials exploring immune checkpoint inhibitors in combination with local therapies.

| NCT | Phase | Study drugs and procedures | Line | Primary endpoint | Estimated end of trial |
|---|---|---|---|---|---|
| NCT02837029 | 1 | Nivolumab + SIRT | Any | MTD | Jul 2020 |
| NCT03033446 | 2 | Nivolumab + SIRT | Any | ORR | Dec 2019 |
| NCT03380130 | 2 | Nivolumab + SIRT | 1 | AEs | Oct 2019 |
| NCT03099564 | 1 | Pembrolizumab + SIRT | 1 | PFS | Jan 2020 |
| NCT03572582 | 2 | Nivolumab + TACE | 1 | ORR | Sep 2022 |
| NCT03397654 | 1B | Pembrolizumab + TACE | 1 | AEs | Dec2019 |
| NCT03143270 | 1 | Nivolumab + debTACE | 1 | AEs | Apr 2019 |
| NCT03638141 | 2 | Tremelimumab(+durvalumab) + debTACE | 1 | ORR | Sep 2020 |
| NCT03203304 | 1 | Nivolumab/ipilimumab + SBRT | 1 | AEs | Aug 2020 |
| NCT03482102 | 2 | Trememumab(+durvalumab) + SBRT | 2 | ORR | Oct 2025 |
| NCT03316872 | 2 | Pembrolizumab + SBRT | 2 | ORR | Apr 2022 |
| NCT01853618 | 1 | Tremelimumab + local ablation | 1 | AEs | Dec 2019 |
| NCT02821754 | 2 | Tremelimumab + local ablation | 1 | PFS | Apr 2021 |
| NCT03630640 | 2 | Nivolumab + electroporation | 1 | RFS | Sep 2020 |

NCT: number of clinical trial (Clinicaltrials.gov); SIRT: selective intra arterial radiation treatment; MTD: maximum tolerated dose; ORR: overall response rate; AEs: adverse events; PFS: progression free survival; TACE: transarterial chemoembolization; debTACE: drug eluting beads transarterial chemoembolization; SBRT: stereotactic body radiation therapy; RFS: recurrence free survival.

## 5. Conclusion

In conclusion immunotherapy for HCC appears to be a very intense field of investigation, raising the hope that new very effective treatment opportunities will become soon available leading to new strategies in the management of patients with HCC. It is currently difficult to make predictions about the precise scenario of immunotherapy for HCC. The trials underway are numerous and their field of application range from the neoadjuvant setting to the second line systemic treatment, passing through the adjuvant and frontline settings. The current scenario is therefore very different from those historically found in Oncology, where a new drug is initially tested in the second line, then in the frontline setting if successful, and only later in the adjuvant and neoadjuvant setting. It is therefore difficult, if not impossible, to make today predictions on possible therapeutic algorithms concerning sequential or simultaneous treatments with tyrosine kinase and immune checkpoint inhibitors. In addition to the results of the individual ongoing trials, other factors will probably be involved in these algorithms. Firstly, the immune checkpoint inhibitors are high-cost drugs and different health systems could implement different algorithms taking into account some economic factors. Secondly, the safety of these drugs is currently regarded as acceptable for patients with an HCC which is in its advanced stage or refractory to regional site treatments. These patients have in fact limited therapeutic perspectives and a poor prognosis in absence of any therapy. The adjuvant setting, in which patients receive the same drugs but with absent or minimal residual disease, requires greater caution and a more careful assessment of the risk of fatal adverse effects. To this extent, the results of the numerous ongoing trials will help to better understand the long-term toxicity profile and therefore to assess whether the risk/benefit ratio is acceptable even in the adjuvant/neoadjuvant setting. Last, but not least, the research of biomarker predictive of response is mandatory to better identify which patients will better respond to immune checkpoint inhibitors and for which patients the treatment would instead be futile. At the moment, the only safe mid term prediction is that immunotherapy will remain one of the hottest topics about HCC treatment in many of its stages.

## Conflict of interests

Francesco Tovoli: consultant for Bayer;

Andrea Casadei Gardini: consultant for Bayer, advisory board for Eisai;

Fabio Piscaglia: speaker for Bayer, Bracco, Eisai, GE, LaForce, Astra Zeneca; advisory board for Tiziana Life Sciences; research contract from Esaote;

Francesca Benevento has no conflicts to declare.

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