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*Review*

# Immune Checkpoint Inhibitors for Unresectable Hepatocellular Carcinoma

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**Abstract:** Despite the advances in screening protocols and treatment options, hepatocellular carcinoma (HCC) is still considered to be the most lethal malignancy in patients with liver cirrhosis. Moreover, the survival outcomes after failure of first-line therapy for unresectable HCC is still poor with limited therapeutic options. One of these options is immune checkpoint inhibitors. The aim of this study is to comprehensively review the efficacy and safety of immune checkpoint inhibitors for patients with HCC.

**Keywords:** HCC; CPI; immunotherapy; survival; progression

## 1. Introduction

Hepatocellular carcinoma (HCC) is still the most common and most lethal malignancy in patients with liver cirrhosis, despite the advances in screening programs, chemoprophylaxis for high-risk patients and treatment options [1,2]. With the rapid increase in prevalence of metabolic disorders, nonalcoholic fatty liver disease became one of the leading risk factors of HCC after hepatitis B and C [3,4]. Overall, HCC is considered an inflammatory prototypic cancer. The high mortality rate from HCC is related to late diagnosis and the concomitant liver dysfunction. In that case, usually, curative resection or liver transplantation is not feasible [5].

Despite the recent advances in systemic therapy for unresectable HCC, patients who progress on first-line multikinase inhibitors, namely sorafenib [which targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR-β) and rapidly accelerated fibrosarcoma (RAF) kinases] [6–8] and lenvatinib (which targets VEGFR1, VEGFR2 and VEGFR3, PDGFR alpha, fibroblast growth factor receptor (FGFR) and KIT and RET tyrosine kinases) [9–13], have limited options [5,14]. Moreover, these systemic therapies are usually associated with significant resistance and side-effects. Furthermore, some clinical trials designed to expand on the already existing options for patients with HCC showed disappointing results [15]. However, recently four additional targeted therapies got approval for treatment of HCC based on phase III randomized controlled trials. Those therapies include lenvatinib as first-line therapy [9] and regorafenib [14,16], cabozantinib [17] and ramucirumab [18] as rescue therapies after failure of sorafenib.

The tumor microenvironment of the HCC is infiltrated with different types of immune cells, mainly T-cells (CD8+, CD4+, Treg), natural killer cells and myeloid cells (myeloid-derived suppressor cells and tumor-associated macrophages). Due to the chronic inflammation and cirrhosis present in most HCC patients, the tumor ecosystem gets complicated affecting the behavior of the tumor and response to treatment. These changes are due to complex interactions between immune cells and tumor cells in the tumor microenvironment conveyed through cytokines and signaling pathways leading to exhaustion of pro-inflammatory immune cells and the dominance of the regulatory leukocytes hindering the anti-tumor response. A study by Yu et al. [19] concluded that improved overall survival was associated with high immune infiltration. The study further identified different immune clusters based on their prognostic value showing that better outcomes were associated with clusters with high levels of T-cells (mainly CD8+) and low levels of macrophages. A subset of tumor-associated macrophages (M1) was shown to be associated with improved outcomes. Poor prognosis is associated with the accumulation of myeloid-derived suppressor cells, tumor-associated macrophages, CD4+/CD25+/FOXP3+ immune-suppressive T-cells(T-reg), exhausted Th1 CD4+, CD8+ T-cells, dysfunctional NK cells and the expansion of Th2 CD4+ T-cells. Immune checkpoint molecules including programmed cell death (PD-1), CD274, cytotoxic T lymphocyte antigen -4 (CTLA-4), lymphocyte activated gene -3 (LAG-3) and IFNG were identified in clusters that had high levels of CD8+ T-cells. However, these clusters were associated with poor prognosis which leads to the assumption that these molecules are implicated in the HCC immune-exhaustion [20]. Therefore, it is assumed that the administration of immune checkpoint inhibitors would be beneficial for these HCC patients. In the United States, accelerated approval has been granted by the Food and Drug Administration (FDA) to two anti-programmed cell death monoclonal antibodies (nivolumab and pembrolizumab) and a combination of nivolumab plus ipilimumab, a monoclonal antibody against CTLA-4, for patients who progressed on sorafenib based on the results of several phase III trials [21–23]. However, data from phase III trial did not show superior efficacy of nivolumab as first-line therapy over sorafenib [24]. Moreover, the results of KEYNOTE 240 which assessed pembrolizumab as second-line therapy compared to placebo did not meet its predetermined level of statistical significance [25]. Therefore, we aimed to review the current evidence in the literature regarding the use of immune checkpoint inhibitors for the treatment of HCC.

## 2. Immune Checkpoint Inhibitors as a First-Line Therapy

### *2.1. PD-1/PD-L1 Inhibition*

Avoiding immune destruction is one of the hallmarks of cancer. The PD-1/PD-L1 pathway plays a pivotal role in this escape mechanism [26]. Studies have shown that PD-L1 is overexpressed in tumor cells in different types of cancers including HCC, which leads to an increase in binding between PD-L1 and PD-1 on T cells within the tumor microenvironment resulting in immune anergy and apoptosis [27,28]. As a result, with overexpression of PD-L1, the tumor continues to grow unchecked which leads to worse prognosis in patients with HCC [28,29]. Interfering with this binding can result in enhancing immune reaction toward the cancer cells. (Figure 1) Therefore, the introduction of monoclonal antibody in the landscape of treatment of HCC has gained accelerated approval for patients who previously progressed on sorafenib based on the results CheckMate 040 trail [21]. However, for first-line therapy, the CheckMate 459 trial compared nivolumab to sorafenib in patients with Child-Pugh A (non-severe liver cirrhosis). Although the objective response rate was higher in the nivolumab group than the sorafenib group, the overall survival and progression-free survival were not significantly different between both groups [24] (Table 1).

**Table 1.** Immune checkpoint inhibitors as first-line therapy for unresectable hepatocellular carcinoma (HCC).

| Study ID | NCT | Study Design, Key Inclusion | Sample Size | OS, Months (95% CI) | PFS Months (95% CI) | Response Rates | Side Effects |
|---|---|---|---|---|---|---|---|
| PD-1/PD-L1 antibodies | | | | | | | |
| CheckMate 459 ESMO October 2019 | NCT02576509 | RCT, CP: A | 743 patients Nivolumab: 371 pts Sorafenib: 372 pts | Nivolumab vs. Sorafenib: OS: 16.4 (13.9–18.4) vs. 14.7 (11.9–17.2) 12 mo (%): 59.7 (54.4–64.6) vs. 55.1 (49.8–60.1) 24 mo (%): 36.8 (31.8–41.8) vs. 33.1 (28.3–38.0) | Nivolumab vs. Sorafenib: 3.7 (3.1–3.9) vs. 3.8 (3.7–4.5) | Nivolumab vs. Sorafenib: ORR: 57 (15%) vs. 26 (7%) Complete response: 14 (4%) vs. 5 (1%) Partial response: 43 (12%) vs. 21 (6%) | Nivolumab demonstrated a favorable safety profile consistent with previous reports. |
| RATIONALE 301 | NCT03412773 | RCT, BCLC stage C or B, CP: A | 674 patients Tislelizumab vs. Sorafenib | Pending | Pending | Pending | Pending |
| Dual immune checkpoint blockade: | | | | | | | |
| HIMALAYA study | NCT03298451 | RCT, BCLC stage C or B, CP: A | 1310 pts, Durvalumab vs. (Durvalumab + Tremelimumab) vs. Sorafenib | Pending | Pending | Pending | Pending |
| Combination with biological therapy: | | | | | | | |
| IMbrave 150 | NCT03434379 | RCT, CP: A | 501 patients Atezolizumab + Bevacizumab: 336 pts vs. Sorafenib: 165 pts | Atezolizumab + Bevacizumab vs. Sorafenib; Overall death: 28.6% vs. 39.4%; HR: 0.58 (95% CI 0.42–0.79) OS: NE vs. 13.2 (10.4—NE) OS at 6 Mo: 84.8% vs. 72.2% | Atezolizumab + Bevacizumab vs. Sorafenib; Overall progression: 58.6% vs. 66.1%; HR: 0.59 (95% CI 0.47–0.76) PFS: 6.8 (5.7–8.3) vs. 4.3 (4.0–5.6) PFS at 6 Mo: 57.5% vs. 37.2% | Atezolizumab + Bevacizumab vs. Sorafenib; % (95% CI) ORR per RECIST 1.1: 27.3 (22.5–32.5) vs. 11.9 (7.4–18) ORR per HCC specific mRECIST: 33.2 (28.1–38.6) vs. 13.3 (8.4–19.6) | Atezolizumab + Bevacizumab vs. Sorafenib; Grade 3–4 complications: 186 (56.5%) vs. 86 (55.1%) |

**Table 1.** *Cont.*

| Study ID | NCT | Study Design, Key Inclusion | Sample Size | OS, Months (95% CI) | PFS Months (95% CI) | Response Rates | Side Effects |
|---|---|---|---|---|---|---|---|
| Combination with biological therapy: | | | | | | | |
| G030140 group F | NCT02715531 | RCT, CP: A | 119 pts<br>Atezolizumab + Bevacizumab: 60 pts vs.<br>Atezolizumab: 59 pts | Atezolizumab + Bevacizumab vs. Atezolizumab<br>Overall death:<br>27% vs. 31%<br>OS: not reached in both groups | Atezolizumab + Bevacizumab vs. Atezolizumab<br>Overall progression:<br>HR:<br>*per HCC mRECIST*:<br>57% vs. 66%,<br>HR: 0.54 (80% CI 0.40–0.74)<br>*per RECIST 1.1:*<br>58% vs. 66%<br>HR: 0.55 (80% CI 0.40–0.74)<br>PFS Mo:<br>*per HCC mRECIST*:<br>5.6 mo (3.6–7.4) vs. 3.4 mo (1.9–5.2)<br>*per RECIST*:<br>5.7 mo (3.5–9.3) vs. 2.0 mo (1.9–3.7) | Atezolizumab + Bevacizumab vs. Atezolizumab<br>ORR per RECIST 1.1:<br>20% (95% CI 11–32) vs. 17% (95% CI 8–29)<br>ORR per HCC mRECIST:<br>27% (95% CI 16–40) vs. 17% (95% CI 8–29) | Atezolizumab + Bevacizumab vs. Atezolizumab<br>Grade 3–4:<br>12 (20%) vs. 3 (5%)<br>The most common grade 3–4 SEs were: hypertension: 3 (5%) vs. none<br>proteinuria:<br>2 (3%) vs. none |
| G030140 group A | NCT02715531 | RCT, CP: A | 104 pts<br>Atezolizumab + Bevacizumab | 57 (55%) still alive at data cut off<br>OS not reached | Per RECIST 1.1:<br>66%; 7.3 months (95% CI 5.4–9.9)<br>Per HCC mRECIST:<br>66%; 7.3 months (95% CI 5.4–9.9) | ORR per RECIST 1.1: n (%; 95% CI)<br>37 (36%; 26–46)<br>ORR per HCC mRECIST:<br>41 (39%; 30–50) | Serious SEs: 25 (24%)<br>The most common serious SEs were upper gastrointestinal hemorrhage, colitis, esophageal variceal hemorrhage and pneumonitis, each occurring in two (2%) patients. |
| COSMIC 312 | NCT03755791 | RCT, BCLC stage C or B, CP: A | 740 pts<br>Cabozantinib + Atezolizumab: 370 pts vs.<br>Cabozantinib: 185 pts vs.<br>Sorafenib: 185 pts | pending | pending | pending | Pending |
| LEAP 002 | NCT03713593 | RCT, BCLC stage C or B, CP: A | 750 pts<br>Pembrolizumab + Lenvatinib vs.<br>Lenvatinib alone | pending | pending | pending | Pending |
| CheckMate 9DW | NCT04039607 | RCT | 1084 pts<br>Nivolumab + Ipilimumab vs. Sorafenib/Lenvatinib | pending | pending | pending | Pending |

**Table 1.** *Cont.*

| Study ID | NCT | Study Design, Key Inclusion | Sample Size | OS, Months (95% CI) | PFS Months (95% CI) | Response Rates | Side Effects |
|---|---|---|---|---|---|---|---|
| Combination with biological therapy: | | | | | | | |
| KEYNOTE 524; AACR April 2019 | NCT03006926 | Single-arm, BCLC stage C or B, CP: A | 104 pts will be recruited, however, the presented results are for 30 pts (6 pts in safety part and 24 pts in efficacy part) Pembrolizumab + Lenvatinib | pending | pending | ORR per mRECIST per investigator: 11 (36.7) per mRECIST per IIR: 15 (50.0%) Per RECIST IIR: 11 (36.7%) | Any-grade treatment-emergent adverse events (TEAEs) occurred in 28 pts (93%); the most common any-grade TEAEs were decreased appetite (63%) and hypertension (60%). 7 (23%) pts discontinued treatment due to TEAEs and no new safety signals were identified. |
| VEGF Liver 100 | NCT03289533 | Single-arm, BCLC stage C or B, CP: A | 22 pts Avelumab + Axitinib | — | PFS: mo (95% CI) *Per RECIST*: 5.5 (1.9–7.3) *Per mRECIST*: 3.8 (1.9–7.3) 6 months PFS: % (95% CI) *Per RECIST*: 35.1% (15.3–55.8%) *Per mRECIST*: 30.9% (12.5–51.5%) | ORR *Per RECIST*: 13.6% (95% CI, 2.9–34.9%) *Per mRECIST*: 31.8% (95% CI, 13.9–54.9%) | The most common grade 3 treatment-related adverse events (TRAEs) (≥10% of patients) were hypertension (50.0%) and hand-foot syndrome (22.7%); no grade 4/5 TRAEs were reported. |
| Kelley 2017, arm five | NCT02519348 | RCT | 433 pts Durvalumab + Tremelimumab vs. Durvalumab vs. Tremelimumab vs. Durvalumab + Tremelimumab (regmine two) vs. Durvalumab + Bevacizumab | — | — | — | — |

CP: Child-Pugh, RCT: Randomized Controlled Trial, RECIST: Response Evaluation Criteria in Solid Tumors, OS: Overall Survival, PFS: Progression-Free Survival, ORR: Objective Response Rate.

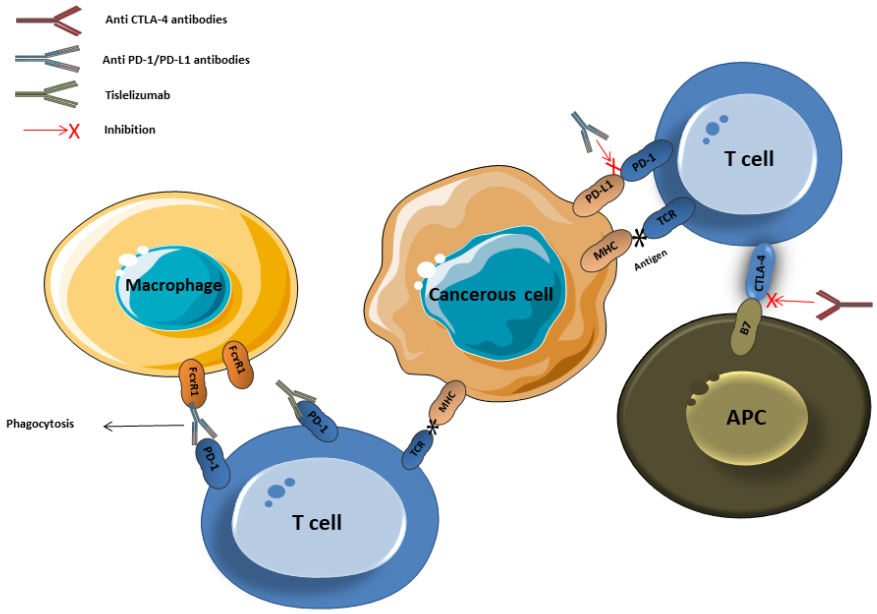


**Figure 1.** Immune checkpoints inhibitors' mechanism of action. PD: programmed cell death, CTLA-4: cytotoxic T-lymphocyte associated protein 4, APC: antigen-presenting cell, MHC: major histocompatibility complex, TCR: T cell.

One of the well-known mechanisms of resistance to anti-PD-1 therapy is FcγR1 mediated macrophage antibody-dependent phagocytosis [30] (Figure 1). Therefore, another monoclonal antibody has been developed to evade the FcγR1 mediated resistance that is, tislelizumab [31]. Clinical data from the RATIONAL 301 trial, which is comparing tislelizumab against sorafenib, supporting this mechanism are still pending [31].

### 2.2. Dual Immune Checkpoint Blockade

CTLA-4 is expressed on T regulatory cells regulating the early immune response after the primary stimulation by antigens mainly in lymphoid organs whereas PD-1 is expressed mainly on activated T cells in the tumor microenvironment regulating late immune response. Moreover, inhibition of the CTLA-4/B7 signal in lymph nodes increases activated CD8+ cells which will subsequently infiltrate the tumor and be part of the microenvironment [32,33]. Based on this, several studies have shown promising results with dual immunotherapy [34,35]. The success achieved in these trials especially in for patients with melanoma [36] has inspired the application of dual immune blockage for other types of cancers including HCC. Therefore, after the success achieved by the phase I/II trial investigating the efficacy and safety of dual immune therapy for patients progressed on sorafenib [37], a comparative randomized controlled trial, HIMALAYA study, was designed to compare Duravalumab versus the combination of Duravalumab plus Tremelimumab versus sorafenib. Its results are still bending (Table 1).

### 2.3. Combination with Biological Therapy

Vascular endothelial growth factor (VEGF) has been linked with the development and progression of HCC [38,39]. Moreover, it has a role in immune suppression as it has been found that it creates an immunosuppressive microenvironment through the recruitment of several inhibitory cells such as T regulatory cells, tumor-associated macrophages and myeloid-derived suppressor cells. Those cells release cytokines such as IL-10 and TGF-β that inhibit natural killer cell and T cell activation and impedes dendritic cell maturation as shown in Figure 2 [33,40,41].

The landmark IMbrave 150 trial comparing atezolizumab (PD-L1 monoclonal antibody) plus bevacizumab (a monoclonal antibody against vascular endothelial growth factor) versus sorafenib found

a better objective response rate and survival for patients treated with the combination therapy [42]. Moreover, the combination of atezolizumab plus bevacizumab showed a better progression-free survival when compared to atezolizumab alone [43]. As the main concern for patients with liver cirrhosis treated with bevacizumab is upper gastrointestinal bleeding, it occurred in 7% of the patients who received the combination therapy which is comparable to earlier reports evaluating bevacizumab alone in patients with HCC [42,44,45]. However, proteinuria and hypertension, as main side effects of bevacizumab, still among the top side effects of combination therapy. However, further evaluation of combination therapy versus sorafenib or lenvatinib as first-line therapy for HCC is still under investigation. For example, the combination of nivolumab plus ipilimumab versus sorafenib/lenvatinib as first-line therapy for HCC is still under investigation by the CheckMate 9DW trial (NCT04039607), the combination of cabozantinib plus atezolizumab versus sorafenib is under investigation by COSMIC 312 trial (NCT03755791) and the combination between pembrolizumab plus lenvatinib versus lenvatinib alone is under investigation by the LEAP 002 trial (NCT03713593). Nevertheless, the success achieved by the landmark IMbrave 150 trial and G030140 trial has a great implication for the practice regarding the upfront therapy for patients with unresectable HCC. Nevertheless, these trials included only patients with early liver disease and the efficacy and safety of the combination therapy in patients with advanced liver disease is still unelucidated. Furthermore, no data available about subsequent therapy after the failure of immune checkpoint. More details are provided in Table 1.

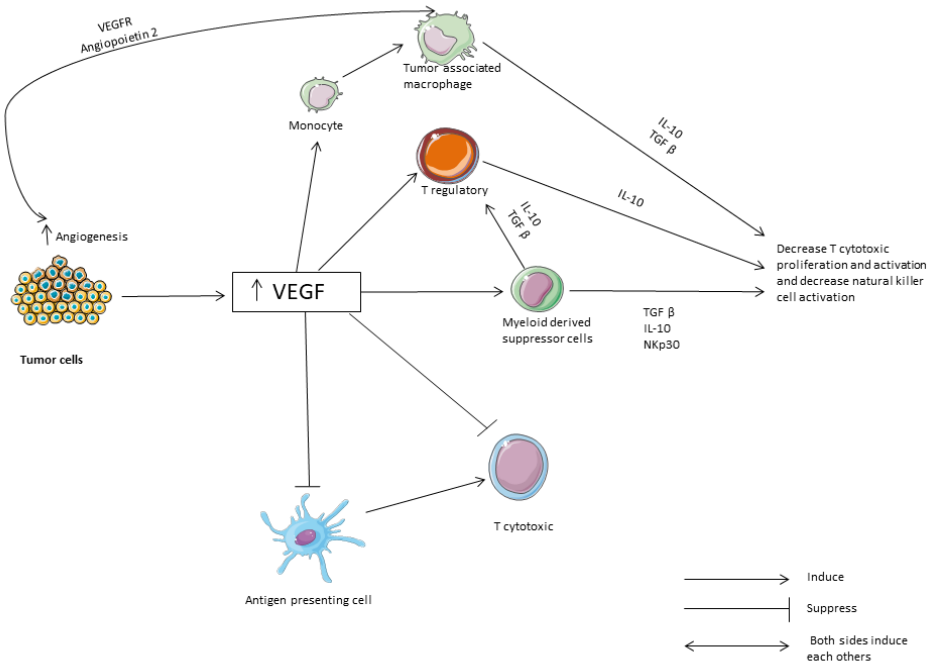


**Figure 2.** The role of VEGF and cytokines in immune suppression. VEGF: vascular endothelial growth factor. TGF: transformation growth factor.

## 3. Immune Checkpoint Inhibitors as Second-Line Therapy

### *3.1. CTLA-4 Inhibition*

Sangro et al. recruited 21 patients with hepatitis C virus who had progressed on previous lines of treatment for HCC. The treatment was tremelimumab at a dose of 15 mg/kg IV every 90 days. The drug showed a safe profile with a partial response rate of 17.6% [46]. Interestingly, the viral load for HCV decreased. Denoting the antiviral effect with the enhanced immunity. Moreover, the addition of ablation therapy to the anti-CTLA-4 showed a higher response rate with a similar safety profile [47] (Table 2).

**Table 2.** Immune checkpoint inhibitors after failure or intolerability for first-line therapy for patients with unresectable HCC.

| Study ID | NCT | Study Design, Key Inclusion | Sample Size | OS, Months (95% CI) | PFS Months (95% CI) | Response Rates | Side Effects |
|---|---|---|---|---|---|---|---|
| CTLA-4 antibodies | | | | | | | |
| Sangro 2013 | NCT01008358 | Single-arm, HCV patients, CP: A or B | 21 pts Tremelimumab | — | — | ORR: 17.6% time to progression: 6.48 months (95% CI 3.95–9.14) | Grade 3–4 transaminase elevation: 45% |
| Duffy 2017 | NCT01853618 | Single-arm, CP: A or B | 32 pts Tremelimumab plus ablation | OS: 12.3 months (95% CI 9.3 to 15.4 months). Six months OS: 85.7% (66.3–94.4%) One year OS: 50.8% (29.1–68.9%) | PFS: 7.4 months (4.7–19.4 months) Six months PFS: 57.1% (37.1–72.9%) One year PFS: 33.1% (16.2–51.2%) | Partial response: 26% (95% CI 9.1–51.2) | Grade 3–4 increase AST: 7 pts (19%) |
| PD-1/PD-L1 inhibition: | | | | | | | |
| KEYNOTE 240 | NCT02702401 | RCT, CP: A | 413 pts Pembrolizumab: 278 pts vs. Placebo: 135 pts | OS: Pembrolizumab: 13.9 months (95% CI, 11.6 to 16.0 months) Placebo: 10.6 months (95% CI, 8.3 to 13.5 months) HR: 0.781; 95% CI, 0.611 to 0.998 | PFS: Pembrolizumab: 3.0 months (95% CI, 2.8 to 4.1 months) Placebo: 2.8 months (95% CI, 1.6 to 3.0 months) HR: 0.718; 95% CI, 0.570 to 0.904 PFS at 12 months: Pembrolizumab: 19.4% (95% CI, 14.6% to 24.9%) Placebo: 6.7% (95% CI, 3.0% to 12.4%) | ORR: Pembrolizumab: 18.3% (95% CI 14–23.4) Placebo: 4.4% (95% CI 1.6–9.4) Estimated treatment difference: 13.8 (95% CI: 7.7 to 19.5) | Any grade 3–4: Pembrolizumab: 52% Placebo: 46.3% Grade 3–4 AST elevation: Pembrolizumab: 13.3% Placebo: 7.5% |
| Scheiner 2019 | NA | Retrospective cohort | 65 pts Nivolumab: 34 pts Pembrolizumab: 31 pts | OS: Nivolumab: 9.0 (95% CI, 5.5–12.5) months Pembrolizumab: 11.0 (95% CI, 7.4–14.5) months 1 year OS: Nivolumab: 38% Pembrolizumab: 44% | PFS Nivolumab: 4.3 (95% CI, 2.0–6.7) months Pembrolizumab: 5.6 (95% CI, 1.1–10.1) months | ORR: Nivolumab: 15% Pembrolizumab: 10% | High grade: 17% in both groups |
| Choi 2020 | NA | Propensity score matching, CP: A | 272 pts after matching Regorafenib: 136 pts vs. Nivolumab: 136 pts | weeks, median (95% CI) Regorafenib: 31.3 (24.6–42.0) Nivolumab: 37.1 (22.4–49.0) | time in weeks; median (95% CI) Regorafenib: 12.6 (10.6–15.7) Nivolumab: 7.1 (6.1–11.1) | ORR: Regorafenib: 3.7% Nivolumab: 14% | |

**Table 2.** *Cont.*

| Study ID | NCT | Study Design, Key Inclusion | Sample Size | OS, Months (95% CI) | PFS Months (95% CI) | Response Rates | Side Effects |
|---|---|---|---|---|---|---|---|
| PD-1/PD-L1 inhibition: | | | | | | | |
| Lee 2020 | NA | Retrospective cohort | 150 patients<br>Regorafenib: 102 patients<br>Nivolumab: 48 patients | OS:<br>Regorafenib: 6.9 months (95% CI, 3.5–13.1)<br>Nivolumab: 5.9 months (95% CI, 3.2–18.1)<br>Death rates:<br>Regorafenib: 37.3%<br>Nivolumab: 56.3% | mTTP<br>Regorafenib: 3.3 months; (95% CI, 2.0–5.3)<br>Nivolumab: 4.0 months; (95% CI, 1.8–8.7)<br>Progression:<br>Regorafenib: 60.8%<br>Nivolumab: 60.4% | ORR:<br>Regorafenib: 5.9%<br>Nivolumab: 16.7% | |
| Yu 2019 | NA | Retrospective cohort | 76 pts<br>Nivolumab alone: 22 pts<br>Nivolumab plus radiotherapy: 54 pts | Patients who had received previous/concurrent RT had a significantly longer progression-free survival (PFS; $p = 0.008$) and overall survival (OS; $p = 0.007$) than those who did not receive RT | — | No complete response<br>PR:<br>Nivolumab alone: 1 pt (4.5%)<br>Nivolumab plus radio: 8 pts (14.8%) | Nivolumab-related toxicities were generally tolerable regardless of the history of RT. |
| Qin 2020 | NCT02989922 | RCT | Total 220 pts<br>Camrelizumab every two weeks group: 111 pts<br>Camrelizumab every three weeks group: 109 pts. | OS:<br>Overall: 13.8 (11.5–16.6)<br>Two months: 14.2 (11.5–NR)<br>three months: 13.2 (9.4–17.0)<br>OS rates:<br>At 6 months, % (95% CI):<br>Overall: 74.4% (68.0–79.7)<br>Two weeks: 75.9% (66.6–82.9)<br>Three weeks: 73.0% (63.6–80.4)<br>At 9 months:<br>Overall: 64.0% (57.2–70.1)<br>Two weeks: 67.3% (57.5–75.3)<br>Three weeks: 60.8% (50.8–69.3)<br>At 12 months:<br>Overall: 55.9% (48.9–62.2)<br>Two weeks: 59.6% (49.6–68.2)<br>Three weeks:52.2% (42.3–61.2) | PFS:<br>Overall: 2.1 months (2.0–3.2)<br>Two weeks: 2.3 months (1.9–3.2)<br>Three weeks: 2.0 months (2.0–3.2)<br>Disease progression rate:<br>Overall: 73%<br>Two weeks: 72%<br>Three weeks: 74% | ORR: Number (%, 95% CI)<br>Overall: 32 (14.7%; 10.3–20.2)<br>Every two weeks: 13 (11.9%; 6.5–19.5)<br>Every three weeks: 19 (17.6%; 10.9–26.1) | Grade 3:<br>Overall: 11 (5.1%)<br>Two weeks: 11 (10.1%)<br>Three weeks: 6 (5.6%)<br>Grade 4:<br>Overall: 5 (2.3%)<br>Two weeks: zero<br>Three weeks: zero (I do not know how both two weeks and three weeks are zero but ht overall is 5)<br>Grade five:<br>Overall: 1 (0.5%), two and three weeks are zero. |

**Table 2.** *Cont.*

| Study ID | NCT | Study Design, Key Inclusion | Sample Size | OS, Months (95% CI) | PFS Months (95% CI) | Response Rates | Side Effects |
|---|---|---|---|---|---|---|---|
| PD-1/PD-L1 inhibition: | | | | | | | |
| CHECKMATE 040 | Dose escalation | Phase I/2 trial | 48 pts<br>Nivolumab | — | — | — | Treatment-related grade 3–4: 25% |
| | Dose expansion | | 214 pts Nivolumab<br>uninfected Sorafenib untreated/intolerant: 56 pts<br>uninfected Sorafenib progressors: 57 pts<br>HCV: 50 pts<br>HBV: 51 pts | OS: not reached<br>6 months OS:<br>Overall: 83% (78 to 88)<br>uninfected untreated/intolerant: 89% (77 to 95)<br>uninfected Sorafenib progressors: 75% (62 to 85)<br>HCV: 85% (72 to 93)<br>HBV: 84% (71 to 92) | PFS:<br>Overall: 4.0 (2.9 to 5.4)<br>uninfected untreated/intolerant: 5.4 (3.9 to 8.5)<br>uninfected Sorafenib progressors: 4.0 (2.6 to 6.7)<br>HCV: 4.0 (2.6 to 5.7)<br>HBV: 4.0 (1.3 to 4.1) | ORR:<br>Overall: 42 (20%; 15 to 26)<br>uninfected untreated/intolerant: 13 (23%; 13 to 36)<br>uninfected Sorafenib progressors: 12 (21%; 11 to 34)<br>HCV: 10 (20%; 10 to 34)<br>HBV: 7 (14%; 6 to 26) | Grade 3–4: (19%) |
| KEYNOTE 224 | NCT02702414 | Single-arm, CP: A | 104 pts<br>Pembrolizumab | OS:<br>12.9 months (95% CI 9.7–15.5)<br>OS at 12 months:<br>54% (95% CI 44–63) | PFS:<br>4.9 months (95% CI 3.4–7.2)<br>PFS at 12 months:<br>28% (95% CI 19–37) | ORR:<br>17% (95% CI 11–26) | Grade 3: 24% |
| He 2018 | NCT02383212 | Single-arm, CP: A | 26 pts<br>Cemiplimab | — | PFS:<br>3.7 months (95% CI: 2.3–9.1) | PR: 19.2%<br>Stable disease: 53.8% | 1 death due to hepatic failure related to treatment |
| | NCT04294498 | Single-arm, HBV, CP: A | 43 pts<br>Durvalumab | — | — | — | — |
| Dual immune checkpoint blockade | | | | | | | |
| Kelley 2017 | NCT02519348 | RCT, here we present the results of initial phase one safety and efficacy analysis | 40 pts<br>Durvalumab/Tremelimumab combination | — | — | ORR: 15% | Most common grade ≥3 related AE was asymptomatic increased AST (10%) |
| Combination with biological therapy: | | | | | | | |
| Bang 2019 | NCT02572687 | Single-arm | 28 pts<br>Ramucirumab and Durvalumab | 10.7 months (95% CI 5.1–18.4) | 4.4 months (95% CI 1.6–5.7) | ORR: 3 (11%) | |
| Xu 2019 | NCT02942329 | Single-arm | 18 pts<br>Camrelizumab + Apatinib | OS: not reached | PFS: 5.8 months (2.6, NR)<br>At 6 months: 45.4% (20.9%, 67.1%)<br>At 9 months: 37.8% (15.0%, 60.7%) | ORR: 44.4% | |

CP: Child-Pugh, RCT: Randomized Controlled Trial, RECIST: Response Evaluation Criteria in Solid Tumors, OS: Overall Survival, PFS: Progression-Free Survival, ORR: Objective Response Rate, TTP: Time to Progression, PR: Partial Response.

### 3.2. PD-1/PD-L1 Inhibition

The progression-free survival, overall survival and response rates were found to be better for patients treated with anti-PD-1/PD-L1 compared to placebo [25]. However, the data from the retrospective analysis did not show differences between anti-PD-1/PD-L1 when compared to regorafenib [48,49]. Interestingly, a combination of anti-PD-1/PD-L1 with radiation therapy showed better progression-free survival and overall survival when compared to anti-PD-1/PDL-1 alone [50] (Table 2).

### 3.3. Dual Immune Checkpoint Blockade

Initial results of a single-arm study examining a combination between durvalumab and tremelimumab in patients with or without hepatitis infection. Out of 40 patients treated, 6 (15%) had an objective response rate with an acceptable safety profile [37] (Table 2).

### 3.4. Combination with Biological Therapy

Two studies evaluated the combination of biologic therapy with immunotherapy. The first evaluated ramucirumab plus duravalumab revealing an objective response rate of 11% and progression-free survival of 4.4 months [51]. The other one evaluated camrelizumab plus apatinib revealing an objective response rate of 44.4% and progression-free survival of 5.8 months [52] (Table 2).

## 4. Predictors of Response Using PD-L1 Expression

Immunohistochemical detection of PD-L1 has been studied in clinical trials as a predictor of response. It has been found that the expression of PD-L1 is associated with better overall response and survival outcomes [21,23]. A high tumor mutation burden (TMB), the number of somatic non-synchronous mutations in the genome of cancer cells, is a known predictive factor for response in different solid tumors. However, HCC has a low TMB compared to other solid malignancies which limited the predictive ability of this marker for HCC [53–55].

## 5. Immune Checkpoint Inhibitors for Subgroups of Patients

### 5.1. Use of Immune Checkpoint Inhibitors in Patients Autoimmune Diseases

One of the main concerns while treating patients with immune checkpoint inhibitors is immune-related adverse events which can be irreversible and even fatal [56–58]. Therefore, patients with a pre-existing auto-immune disease usually excluded from clinical trials [42], and, as a consequence, data about safety profiles in these populations is not available. However, liver cirrhosis can develop due to autoimmune diseases such as primary sclerosing cholangitis, autoimmune hepatitis, primary biliary cholangitis and so forth [59,60]. And, patients with HCC may suffer from another non-hepatobiliary autoimmune disease. Thus, understanding the underlying pathophysiological mechanisms and its interaction with the immune checkpoints' pathways is crucial in order to provide these patients with the therapeutic advantages without devastating side effects.

Several retrospective studies and case reports evaluated the safety profile of immune checkpoint inhibitors for patients with cancer and concomitant autoimmune disease [61–68]. Abdel-Wahab et al. conducted a systematic review evaluating the safety of immune checkpoint in patients with preexisting autoimmune disease and they found that; although some events may be severe and even fatal, most immune flares and immune-related side effects are managed without permanent drug discontinuation. However, for patients with neurological diseases such as myasthenia graves and multiple sclerosis, almost all patients developed exacerbation or immune-related side effects. Therefore, careful evaluation should be considered before prescribing immune checkpoints inhibitors for patients with neurological autoimmune diseases [61]. In a more recent large scale study, patients with a preexisting autoimmune disease treated with immune checkpoints had a higher risk of immune-related side effects than the

control group. Furthermore, active disease and female gender were found to be independent predictors for the development of immune-related side-effects [62].

In summary, the immune-related side effects seem to be higher in patients with pre-existing autoimmune disease. Active disease and female gender are independent risk factors for immune-related side effects. Although immune-related side effects in patients treated with immune checkpoint inhibitors with a pre-existing autoimmune disease can be fatal, most cases are managed successfully without permanent discontinuation of the immune checkpoints. Nevertheless, these observations are derived from case reports and small retrospective studies and a well-designed large scale trial still represents an unmet need. Moreover, data about patients with HCC carcinoma specifically and hepatobiliary autoimmune diseases is still sparse.

### *5.2. Use of Immune Checkpoint Inhibitors in Patients with Inflammatory Bowel Disease*

Patients suffering from inflammatory bowel disease (IBD) usually suffer from other hepatobiliary diseases such as drug-induced liver injury (about 30% of patients with IBD), primary sclerosing cholangitis (1.4% to 7.5% of patients with IBD), autoimmune hepatitis, primary biliary cirrhosis and nonalcoholic steatohepatitis [69]. These factors, along with the other traditional risk factors, can lead to HCC either directly or indirectly through liver cirrhosis [59]. Therefore, some patients who will suffer from HCC will have a concomitant IBD in which, as discussed before, immune checkpoint inhibitors with or without biologic therapy may be an option. However, the safety of immune checkpoint in this particular population is an ongoing and unanswered question. As known, the CTLA-4 and PD-1/PD-L1 signaling are crucial for gut homeostasis [70,71]. Interestingly, defects in the CTLA-4 gene or overexpression of PD-1/PD-L1 on intestinal epithelium were found to be higher in patients with IBD [72–74]. Figure 3 Therefore, in murine models, it was not surprising that the blockade of these pathways led to CD8 autoimmune enteritis [75]. And, it is not uncommon for a patient treated with immune checkpoint inhibitors to suffer from diarrhea [76]. Thus, IBD exacerbation during treatment with immune checkpoint inhibitors is a theoretical risk. Indeed, evidence about this question started to emanate from high volume centers. For example, in a recently published case series from Mayo Clinic, thirteen patients with a pre-diagnosed IBD were treated with immune checkpoint inhibitors and of them flare occurred in 4 patients (31%) [77]. This observation was also noted in a previous cohort in which 36% of patients with IBD treated with immune checkpoint inhibitors permanently discontinued them for IBD flare [68]. From a larger sample size study, data from a multicenter retrospective analysis included 102 patients with IBD treated with immune checkpoint inhibitors. Overall gastrointestinal side effects occurred in 42 patients (41%) after a median 62 days compared to 11% without IBD. Moreover, about 21% of patients with IBD treated with immune checkpoint inhibitors suffered from grade 3–4 diarrhea and 4 patients (3.9%) had intestinal perforation two of them had surgery [78]. Of note, the rate of intestinal perforation in patients receiving immune checkpoint inhibitors without concomitant IBD has been reported to be about 2.2% [79]. Importantly, most (~90%) of the included patients, in the aforementioned study evaluating the safety of immune checkpoints in patients with IBD, received a monotherapy of immune checkpoint inhibitors, only 10 patients (~10%) received a combination of two immune checkpoint inhibitors and none of the included patients received biologic therapy [78].

The combination of biologic therapy, especially bevacizumab, with immune checkpoint inhibitors in patients with IBD is of particular importance. Indeed, in patients not suffering from IBD, the intestinal perforation rate after using bevacizumab is about (1.5 to 2.5%) and severe bleeding is about 3% [80,81]. Importantly, the mortality rate for patients who develop intestinal perforation due to bevacizumab is high (up to 16%) [80,81]. Thus, even in non-gastrointestinal malignancies, the treatment with bevacizumab was found to be independently associated with a high risk of gastrointestinal perforation [82,83]. Indeed, the evidence about the safety of bevacizumab in patients with IBD is still lacking. Importantly, in patients with HCC, liver cirrhosis is common and gastrointestinal

bleeding especially esophageal varices is a major concern, especially when selecting bevacizumab for treatment [84].

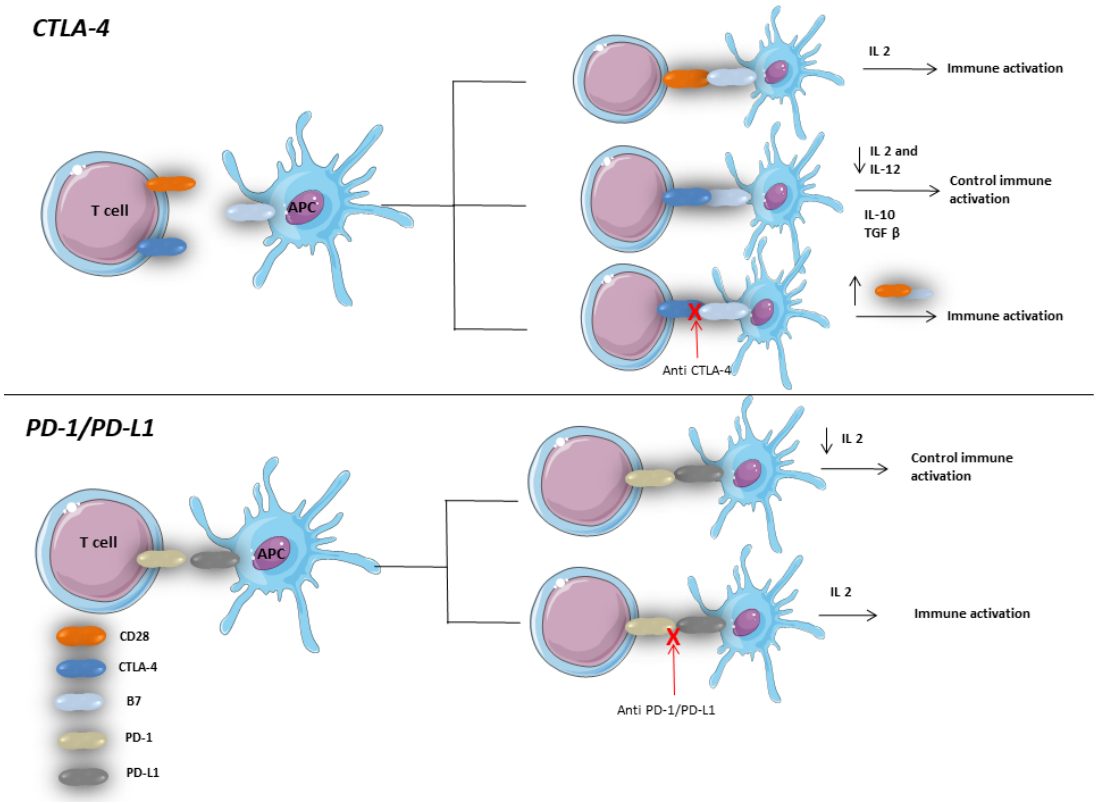


**Figure 3.** Role of CTLA-4 and PD-1/PD-L1 pathways in immune response regulation in gastrointestinal tract. APC: antigen-presenting cells.Both CD28 and CTLA-4 compete with each other for a binding site (B7) on the surface of APC. Binding of CD28 to B7 is associated with induction of immune response through upregulation of production of IL2. On the other side, CTLA-4 B7 binding regulates the late immune response by decreasing IL2 [71]. Therefore, inhibition of CTLA-4 by antiCTLA-4 antibodies was found to be associated with an exaggerated immune response which might lead to colitis [85,86]. PD-1/PD-L1 binding leads to immune response regulation through PI3K and AKT pathways. Therefore, inhibition of this binding might lead to immune response dysregulation which might lead to colitis and autoimmune exacerbation [87].

Overall, the use of atezolizumab with bevacizumab in patients with IBD carries a risk for intestinal perforation, gastrointestinal bleeding and the safety profile is still lacking in the literature.

## 6. Novel Immunotherapies

With the recent advances in the immunotherapeutic mechanisms, novel immunotherapies have gained popularity. Different therapeutic targets have been evaluated such as lymphocyte activation gene 3 (LAG-3). LAG-3 is first described by Triebel et al. and thereafter it was found to be overexpressed on the activated T cytotoxic and T regulatory cells with a negative impact on T helper cells. Therefore, during tumorigenesis, cancer cells use this pathway to escape from the immune system. Therefore, immunoglobin against LAG-3 has been investigated in different clinical trials [88]. Several other novel targets including T cell immunoglobulin and ITIM domain (TIGIT), T cell immunoglobulin and mucin domain-containing -3 (TIM-3) and B and T lymphocyte attenuator (BTLA) have been evaluated in clinical trials [88]. The current ongoing phase II trial [NCT03680508] is designed to evaluate the efficacy of TIM-3 in combination with PD-1 antibody for patients with HCC with no results published yet.

One other therapeutic target is the killer immunoglobulin-like receptor (KIR) which has an inhibitory effect on the NK cells. Therefore, Lirilumab, a KIR antibody, is under investigation in combination with immune checkpoint inhibitors in clinical trials [89].

Overall, the novel immunotherapies' investigation in HCC is still restricted to being a part of evaluation of their role in solid tumors in general. Therefore, a better understanding of these pathways and their contribution to the HCC microenvironment is needed.

## 7. Conclusions

Hepatocellular carcinoma treatment represents a real challenge in patients with cirrhosis and several pharmacological [72–75] and loco-regional [76–81] therapies have been tested with mixed results. A combination of immune checkpoint inhibitors with biologic therapy seems to be promising for a new therapeutic standard of care for patients with unresectable HCC. However, for the subset of patients such as patients with preexisting autoimmune disease, inflammatory bowel disease or nonalcoholic steatohepatitis, the safety and efficacy are still not well established and further studies are needed to address all these open unanswered questions.

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