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REVIEW

Review of immune therapy in HCC: Where are we now and what is the future?

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INTRODUCTION

HCC represents the most common type of primary liver cancer, arising within a background of chronic liver disease and cirrhosis. The most frequent causes include metabolic syndrome, viral infection, alcohol abuse, and aflatoxin exposure. Systemic therapy is the only available treatment for patients with intermediate Barcelona Clinic Liver Cancer (BCLC) stage B (multiple nodules without vascular invasion or extrahepatic metastasis) not suitable for locoregional treatment, and advanced BCLC stage C disease (vascular invasion or extrahepatic metastasis and cancer-related symptoms). After over a decade of multi-kinase inhibitor monopoly, immunotherapy has become an integral part of HCC management. Immune checkpoint inhibitors (ICIs) revert the immunosuppressive tumor microenvironment, whereas their combination with anti-angiogenic drugs, such as anti-VEGF agents and tyrosine-kinase inhibitors, contributes to the suppression of regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages[1] (Figures 1, 2). ICIs are mainly represented by anti-programmed death 1 and its ligand (programmed death ligand 1), and anti-cytotoxic T-lymphocyte antigen 4.

In this review, we aim to summarize the current indications of ICIs for HCC treatment and address the ongoing research in this field (Figure 3).

BCLC B and C

The multikinase inhibitor sorafenib has represented the first-line standard of care for over a decade. However, more recently, atezolizumab plus bevacizumab (anti-programmed death ligand 1 plus anti-VEGF) in the phase 3 IMbrave150 trial and durvalumab plus tremelimumab (STRIDE regimen: anti-programmed death ligand 1 plus anti-cytotoxic T-lymphocyte antigen 4) in the phase 3 HIMALAYA trial demonstrated a statistically significant overall survival (OS) advantage versus sorafenib (atezolizumab plus bevacizumab: HR for death 0.66; 95% CI, 0.52–0.85; $p < 0.001$. STRIDE: HR for death 0.78; 95% CI, 0.67–0.92; $p = 0.0037$). Therefore, they are the preferred first-line regimens for patients with BCLC stage B HCC unsuitable for locoregional therapy or BCLC C, Child-Pugh class A liver function, and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1. Atezolizumab plus bevacizumab achieved a longer median OS (19.2 mo), whereas STRIDE yielded better long-term results, with OS rates of 30.7% and 25.2% at 36 and 48 months, respectively.[2–5] There are no prospective clinical trials directly comparing the 2 regimens. As a result, the choice between the 2 regimens is guided by patients' characteristics and comorbidities, as well as local marketing authorizations.

Combinations of ICIs and tyrosine-kinase inhibitors have not proved to be effective, with the exception of camrelizumab plus rivoceranib in the phase 3 CARES-310 study. Median OS was 22.1 months versus 15.2 months with sorafenib (HR, 0.62; 95% CI, 0.49–0.80; $p < 0.0001$), although the combination was associated with a non-negligible rate of grade 3-4 adverse events (AEs) of 80.5%.[6] Single-agent immunotherapy with either durvalumab in the HIMALAYA trial or tislelizumab in the phase 3 RATIONALE-301 study was noninferior to sorafenib, with a better safety profile

Abbreviations: AE, adverse event; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor.

(grade ≥3 AEs 22.2% with tislelizumab, 37.1% with durvalumab, and 53% with sorafenib).[4,7]

The results of frontline nivolumab plus ipilimumab versus sorafenib or lenvatinib (NCT04039607) are awaited.

In the second-line setting, pembrolizumab and nivolumab plus ipilimumab received the approval of the US Food and Drug Administration after prior sorafenib, based on phase 2 studies.[1]

ADJUVANT SETTING

The IMbrave050 trial was the first phase 3 study to show positive outcomes of adjuvant systemic treatment in patients with high-risk HCC after curative surgery or radiofrequency/microwave ablation. Atezolizumab plus bevacizumab showed an improved recurrence-free survival over active surveillance (HR, 0.72; 95% CI, 0.53–0.98; $p = 0.012$).[8] Based on these results, this combination is now recommended by the American Association for the Study of Liver Diseases in the adjuvant setting. However, the follow-up is still short (17 mo) which means that longer-term OS data are needed. Moreover, safety is a central issue to be addressed, considering the higher rate of grade 3-4 AEs in the experimental arm (41%) compared with the surveillance group (13%). Overall, hypertension (18 vs. 1%) and proteinuria (9% vs. 0%) were the most common grade 3-4 AEs. In the adjuvant setting, durvalumab versus durvalumab plus bevacizumab versus placebo (NCT03847428), nivolumab versus placebo (NCT03383458), and pembrolizumab versus placebo (NCT03867084) are currently under evaluation.

NEOADJUVANT SETTING

Promising early trials assessed ICI-based regimens in the neoadjuvant setting, with the advantage of evaluating treatment response directly on tumor tissue. Notably, neoadjuvant cemiplimab was evaluated in a phase 2 trial enrolling 20 patients undergoing surgery after 2 cycles of immunotherapy.[9] Efficacy outcomes were encouraging, with 15% of partial responses and 85% of patients maintaining stable disease. The rate of grade 3-4 AEs was 10%, with maculopapular rash and pneumonitis being the most common ones.

Moreover, both perioperative nivolumab and nivolumab plus ipilimumab were demonstrated to be safe and feasible in a phase 2 trial. Grade 3-4 AEs were higher with nivolumab plus ipilimumab (43%) than nivolumab alone (23%), but no patients in either group had delayed surgery due to AEs. The median progression-free survival was 9.4 months (95% CI, 1.47–not estimable)

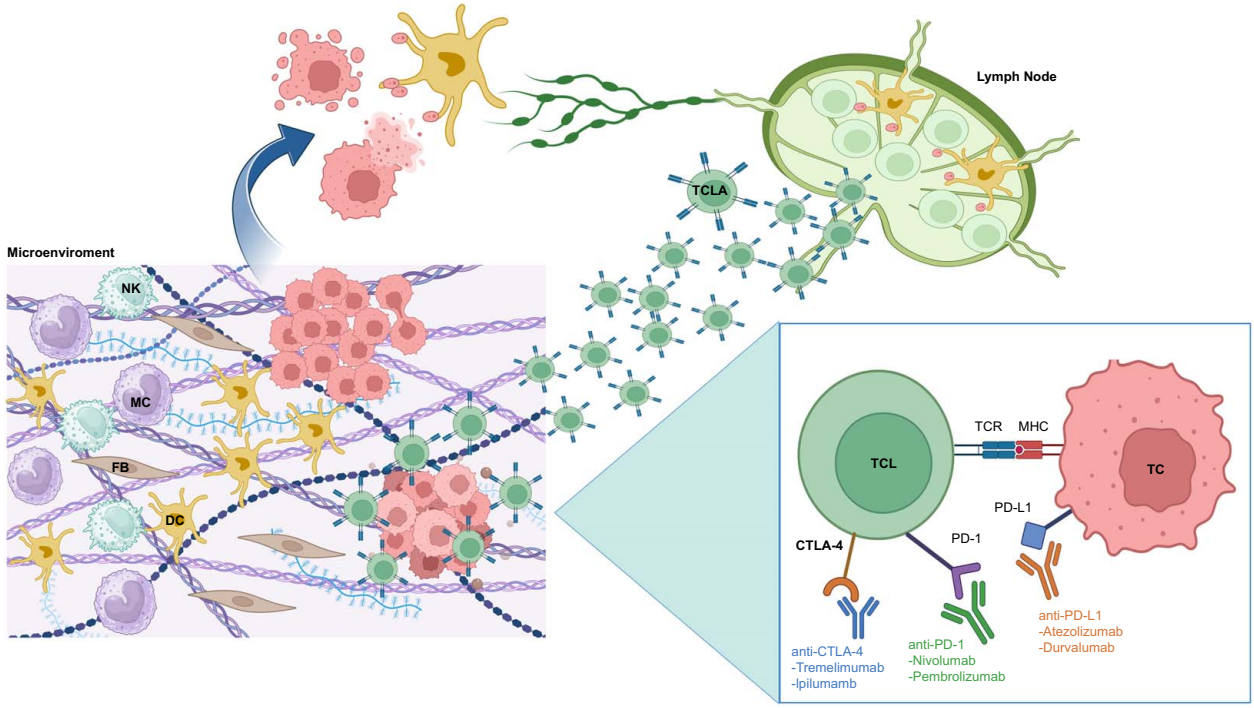

FIGURE 1 Immune microenvironment in HCC. A detailed description of cell populations in the HCC microenvironment and their interaction with cancer cells. Migration of antigen-harboring DCs in draining lymph nodes results in T-cell lymphocyte activation (known as priming), which, in turn, migrates to the tumor site and induces cell-mediated killing. The interaction between activated TCLA and cancer cells is shown along with main immune checkpoints and corresponding inhibitory drugs. Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen 4; DC, dendritic cell; FB, fibroblast; MC, monocytic cell; MHC, major histocompatibility complex; NK, natural killer; PD-1, programmed death 1; PD-L1, programmed death ligand 1; TC, tumor cell; TCL, T-cell lymphocyte; TCLA, T-cell lymphocyte activated; TCR, T-cell receptor. Created with BioRender.com.

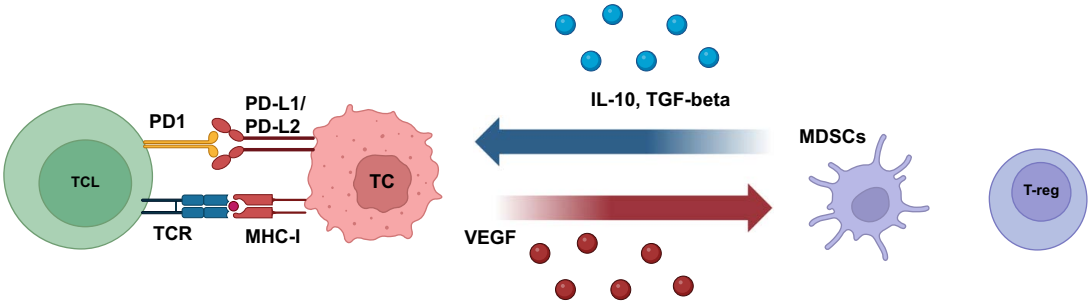

FIGURE 2 Cross-talk between angiogenesis and the immune system. VEGF secreted by cancer cells induces the release of inhibitory cytokines, such as IL-10 and TGF-beta, by T-reg cells and MDSCs, ultimately increasing the PD-1-PD-L1 signaling. As a result, HCC escapes the cell-mediated immune response. Abbreviations: MHC-I, major histocompatibility complex I; MDCSs, medullary dendritic stem cells; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PD-L2, programmed cell death protein ligand 2; TC, tumor cell; TCL, T-cell lymphocyte; TCR, T-cell receptor; T-reg, T-regulatory. Created with BioRender.com.

with nivolumab and 19.5 months (95% CI, 2.33–not estimable) with nivolumab plus ipilimumab (HR 0.99; 95% CI, 0.31–2.54).[10]

DISCUSSION

Immunotherapy represents the new backbone of advanced HCC treatment and may have a role in patients with earlier stages of the disease. However, there are no identified, clinically relevant biomarkers or clinical factors that can guide the choice of an ICI-based treatment and predict a patient's response. Moreover, very little is known about tumor heterogeneity, which may influence treatment response, which is limited only to a subgroup of patients. Therefore, therapeutic selection still relies on patients' baseline features and comorbidities, as well as the toxicity profile of the drugs. On the other hand, immune-related AEs should be carefully evaluated and promptly managed to favor treatment adherence and avoid treatment discontinuation due to the observed positive correlation between longer OS and the development of AEs (Figure 4).

In clinical practice, antiangiogenic agents are contraindicated in patients with varices at high risk for bleeding, whereas ICIs are contraindicated in patients with severe autoimmune diseases due to the risk of exacerbation of their preexisting condition. In addition, they are not recommended in patients with prior liver transplants outside of a clinical trial or protocol due to the risk of graft rejection. Therefore, their use in this setting should only be considered in selected patients, with no alternative therapeutic options, after carefully weighing the risk-benefit ratio. Considering the increasing number of indications for ICIs even in the earlier stages of disease, the most appropriate timing of transplantation in the treatment algorithm will need to be reconsidered.

Furthermore, ICIs are considered safe only in patients with well-preserved liver function, limiting their

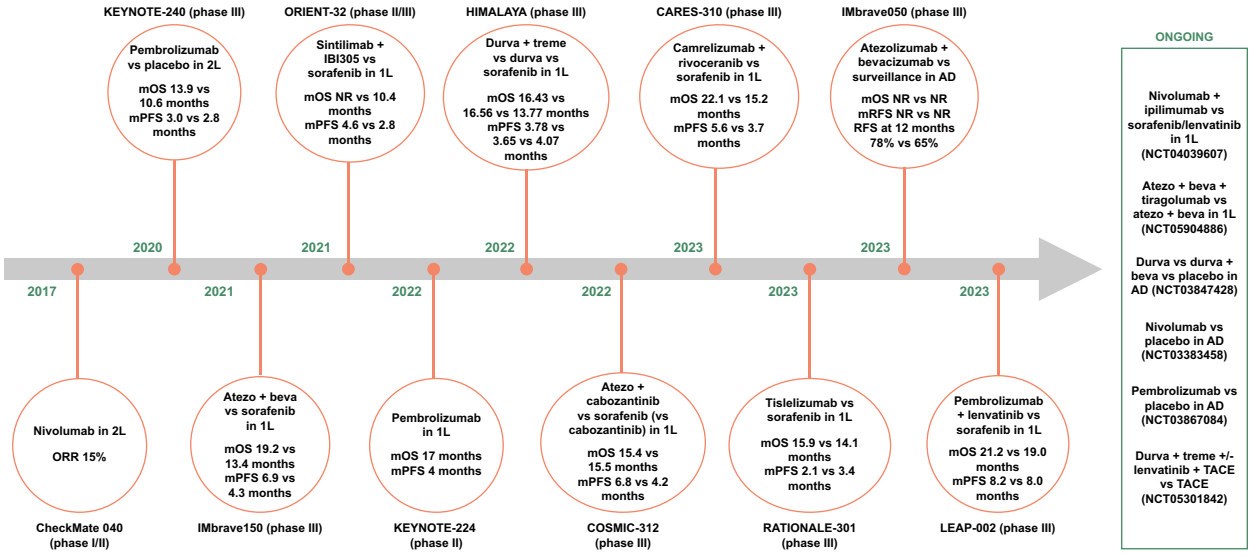

FIGURE 3 Key clinical trials of ICIs for HCC. Abbreviations: 1L, first line; 2L, second line; AD, adjuvant; atezo, atezolizumab; beva, bevacizumab; durva, durvalumab; ICIs, immune checkpoint inhibitors; NR, not reached; treme, tremelimumab. Created with BioRender.com.

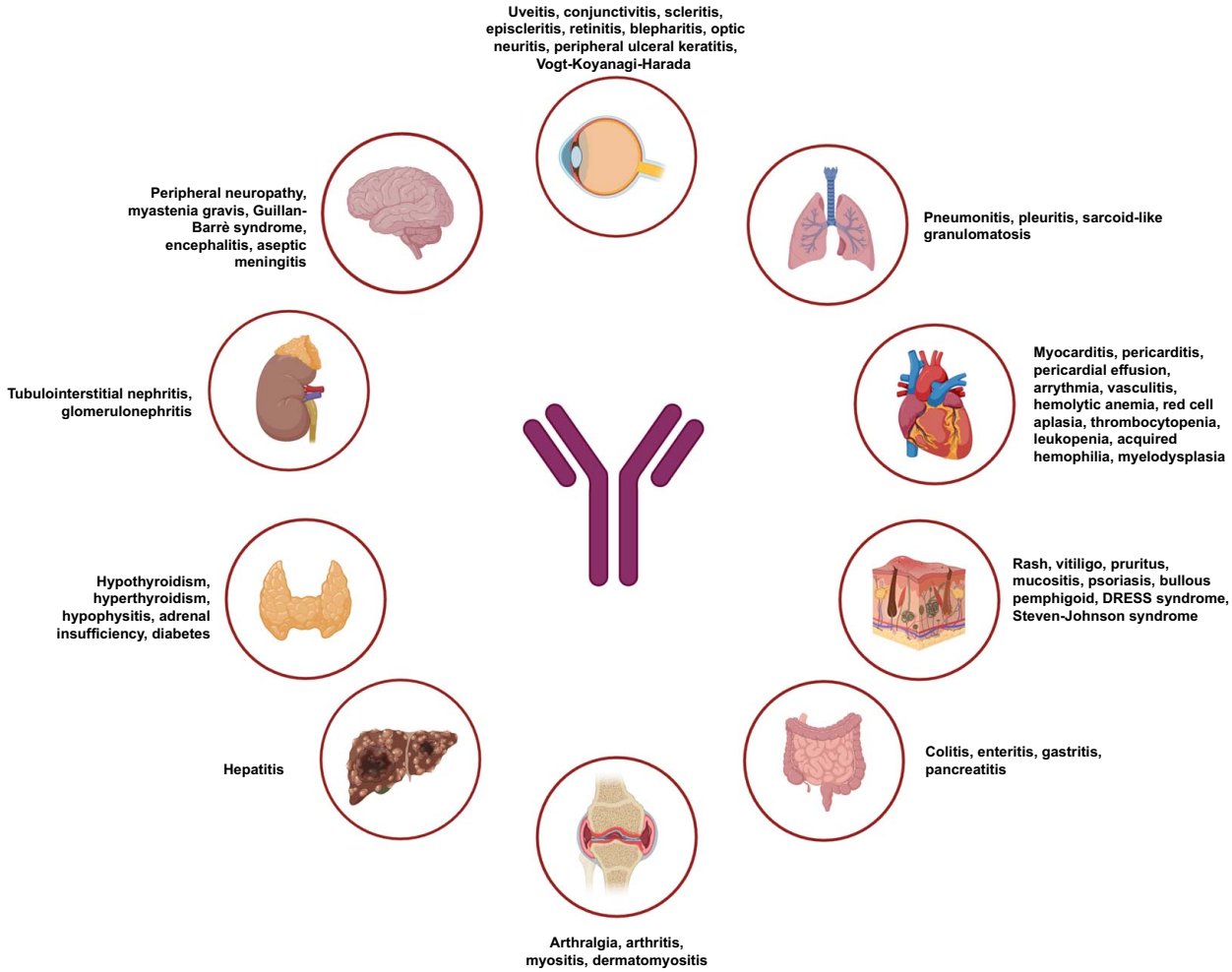

FIGURE 4 Immune-related adverse events. Created with BioRender.com.

application to patients with Child-Pugh B liver function who represent a relevant quote in clinical practice. Currently, data about this patient group derive from retrospective observational studies, in which objective response rates and AEs were comparable among patients with Child-Pugh class A and B liver function, but the latter had worse survival outcomes, confirming the worse prognosis despite clinical activity.[11] Further data may come from ongoing studies, such as SIERRA, which is a phase 3b trial assessing durvalumab plus tremelimumab in patients with ECOG PS 2 or Child-Pugh class B liver function (NCT05883644).

Increasing research has been focusing on the mechanisms of resistance to immunotherapy, that can involve either cancer cells (intrinsic) or the surrounding tumor microenvironment (extrinsic). Patients could be primary nonresponders or may develop acquired resistance after a period of response to immunotherapy. Primary and secondary resistance are associated with reduced tumor immunogenicity and acquisition of a lower immunogenic phenotype after starting treatment, respectively.

Upon progressive disease, there is no evidence about the correct treatment sequence. Rechallenge with ICIs is currently under investigation based on preliminary retrospective data.

In the intermediate stage, immunotherapy is currently being tested in combination with or versus locoregional therapy. Of note, the combination of durvalumab, bevacizumab, and transarterial chemoembolization demonstrated a statistically significant improvement in progression-free survival versus transarterial chemoembolization alone in patients eligible for embolization in the EMERALD-1 phase 3 trial (HR, 0.77; 95% CI, 0.61–0.98; $p = 0.032$),[12] and further studies are ongoing in the same setting (NCT05301842, NCT04246177, NCT04268888, NCT04712643, NCT04803994, NCT04777852, and NCT04224636).

Furthermore, the significant responses reported with immunotherapy regimens are pushing physicians toward unforeseen barriers such as conversion therapy to potentially curative liver surgery or transplantation. The results from the ImmunoXXL study (NCT05879328), which is assessing the feasibility of liver transplant in patients with BCLC B HCC downstaged with first-line atezolizumab and bevacizumab are eagerly awaited.

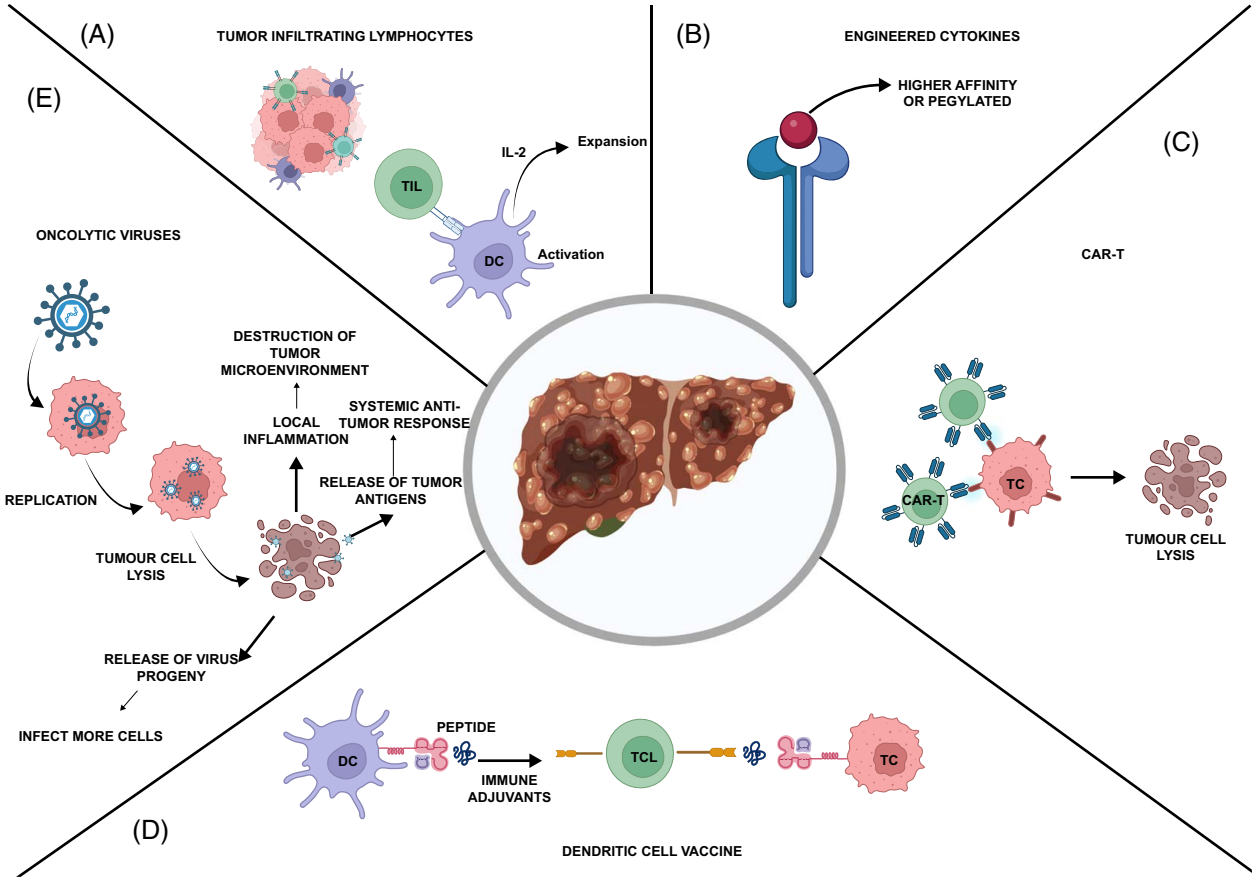

FIGURE 5 Future therapeutic perspectives. (A) TILs are extracted from the microenvironment of the patient's tumor, expanded in vitro with IL-2 and "feeder cells," then re-infused after the patient has undergone lymphodepletion. They can stimulate a cell-mediated immune response against cancer cells. (B) Cytokines promoting the killing activity of cytotoxic T cells and natural killer lymphocytes (eg, IL-2) can be engineered to have higher affinity for their own receptor or PEGylated to prolong their circulation half-life. (C) CAR-T cells are engineered to express receptors that target specific tumor antigens: cells are collected from a patient through leukapheresis, and T-cell lymphocytes are isolated. T cells are transfected with a retroviral vector that carries the gene encoding a chimeric antigen receptor transgene. (D) DC vaccines prime naïve T cells, inducing transition to cytotoxic T lymphocytes that can eliminate cancer cells by recognizing specific antigens. (E) Oncolytic viruses infect malignant cells, undergo a series of replication cycles, and are released through cell lysis to infect other tumor cells. Moreover, oncolysis induces both local inflammation and a systemic immune response through the release of tumor antigens. Abbreviations: CAR-T, chimeric antigen receptor T cells; DC, dendritic cell; TC, tumor cell, TCL, T-cell lymphocyte; TILs, tumor-infiltrating lymphocytes. Created with BioRender.com.

Lastly, novel immunotherapy targets, immune cells modified with chimeric antigen receptors, peptide- and dendritic cell–based therapeutic cancer vaccines, oncolytic viral therapy, adoptive cell therapy, as well as engineered cytokines are promising strategies and may potentially lead to a personalized treatment (Figure 5).

CONCLUSIONS

Durable remission and complete tumor responses, together with a good safety profile are key objectives of any anticancer treatment, and also of immunotherapy, which has revolutionized the current HCC treatment scenario and patients' prognosis. Further steps are needed to overcome treatment resistance, establish the most appropriate treatment sequence, identify reliable predictive and prognostic biomarkers, and increase the proportion of patients potentially benefitting from immunotherapy.

CONFLICTS OF INTEREST

Lorenza Rimassa consults for, is on the speakers' bureau for, and received grants from AstraZeneca, Eisai, Incyte, Ipsen, Roche, and Servier. She consults for and is on the speakers' bureau for Bayer and BMS. She consults for and received grants from Exelixis, MSD, Nerviano Medical Sciences, and Zymeworks. She consults for Basilea, Elevar Therapeutics, Genenta, Hengrui, IQVIA, Jazz Pharmaceuticals, and Taiho Oncology. She is on the speakers' bureau for Merck Serono. She received grants from Agios, BeiGene, Fibrogen, and Lilly. The remaining authors have no conflicts to report.

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