Challenges of combination therapy with immune checkpoint inhibitors for hepatocellular carcinoma

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Summary
Immune checkpoint inhibitor (ICI) therapy targeting anti-programmed cell death-1 (anti-PD-1) or its ligand (anti-PD-L1) is the backbone of numerous combination regimens aimed at improving the objective response and survival of patients with hepatocellular carcinoma (HCC). Clinical trials of immunoncology regimens in other cancer types have shed light on issues of study design, including how to choose candidate regimens based on early-phase trial results, statistical considerations in trials with multiple primary endpoints, and the importance of predictive biomarkers. In this review, the updated data from early-phase trials of combination immunotherapy for HCC are summarised. Since the most extensively tested combination regimens for advanced HCC comprise anti-PD-1/anti-PD-L1 agents plus antiangiogenic agents, the relative benefit and antitumor mechanism of antiangiogenic multikinase inhibitors versus specific VEGF/VEGFR inhibitors are discussed. Other critical issues in the development of combination immunotherapy, including optimal management of immune-related adverse events and the value of ICI therapy in combination with locoregional treatment for HCC, are also explored.

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Introduction
Immune checkpoint inhibitor (ICI) therapy, particularly antibodies targeting the programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathway, has represented a major breakthrough in drug development for oncology in the past decade. Anti-PD-1 or anti-PD-L1 monotherapy has been approved for the treatment of more than 10 cancer types, with objective response rates (ORRs) of 15–20% and good safety profiles.1,2 The broad-spectrum antitumor activity and good tolerability of anti-PD-1/anti-PD-L1 therapy also make it the backbone of a burgeoning number of clinical trials testing combination regimens with other immunomodulatory agents or conventional systemic anticancer therapy, including cytotoxic chemotherapy or molecular targeted therapy.3 Superior progression-free survival or overall survival of combination therapy, demonstrated by randomised clinical trials, has led to the approval of anti-PD-1 plus anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA4) for the treatment of advanced melanoma, renal cell carcinoma (RCC), and colorectal cancer with microsatellite instability;4–6 anti-PD-1 plus an antiangiogenic for renal cell carcinoma;7 and anti-PD-1/anti-PD-L1 plus cytotoxic chemotherapy for non-small cell lung cancer and triple negative breast cancer.8,9

ICI therapy is also an attractive approach for new drug development in hepatocellular carcinoma (HCC). For anti-PD-1 ICI, both nivolumab and pembrolizumab were granted accelerated approval by the US Food and Drug Administration (FDA) based on efficacy data obtained from single-arm clinical trials: The ORR and median overall survival (OS) were approximately 15% and 1 year, respectively, in patients previously treated with sorafenib.10,11 For anti-CTLA4 ICI, tremelimumab was tested in a small cohort of hepatitis C-related HCC and demonstrated an ORR of 17.6% (3 partial responses in 17 evaluable patients), a median time to progression of 6.48 months, and a decrease in HCV viral loads during tremelimumab treatment.12 Although the incidence of hepatic events in HCC is slightly higher than in other cancer types, most of the toxicities are manageable with an exceedingly low rate of liver failure.

Despite the initial enthusiasm around anti-PD-1 therapy for HCC, randomised trials of anti-PD-1 monotherapy in either first-line (nivolumab vs. sorafenib)13 or second-line (pembrolizumab vs. placebo)14 settings did not demonstrate statistically significant improvement in OS. Therefore, development of combination strategies has become an even more urgent need to improve treatment efficacy for HCC. Many recent clinical trials testing the same combination immunotherapy in multiple cancer types, the so-called basket trial design, included HCC as a cancer type of interest.15 Preliminary results from early-phase clinical trials indicated superior response rates and duration of response when anti-PD-1 or anti-PD-L1 agents were combined with anti-CTLA4 or antiangiogenic molecular targeted therapy (Table 1).

In this review, the recently reported trials of combination immunotherapy for HCC are summarised, focusing on the study design and interpretation of efficacy and safety results. Examples of successful clinical trials from other cancer types will also be discussed to illustrate the opportunities and challenges of developing combination immunotherapy for HCC. Challenges common to
Promising data on immuno-oncology combinations for advanced HCC

The most extensively tested combination regimen for advanced HCC comprises anti-PD1/anti-PDL1 plus antiangiogenic agents. All of the approved targeted therapies for the treatment of advanced HCC (sorafenib and lenvatinib in the first line; regorafenib, cabozantinib, and ramucirumab in the second line) have antiangiogenic effects that are considered critical for antitumor efficacy in HCC.

In recent years, both pre-clinical models and clinical trials demonstrated the immunomodulatory effects of antiangiogenic agents in the tumour microenvironment, including enhancement of dendritic cell maturation, T cell trafficking and function, and reversal of immunosuppression caused by tissue hypoxia and immunosuppressive cells, such as tumour-associated macrophages (TAMs), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs). The combination of ICIs and antiangiogenics has been tested most extensively in patients with advanced RCC, leading to the approval of pembrolizumab plus axitinib as first-line therapy in early 2019, based on superior OS (hazard ratio 0.53) and progression-free survival (PFS) (hazard ratio 0.69) compared with the prior standard therapy sunitinib. ORRs of similar combination therapies ranged between 40% and 60% in advanced RCC, and treatment-related adverse events were generally manageable.

Most of the recently reported early-phase trials of anti-PD-1/anti-PD-L1 plus antiangiogenic agents for advanced HCC were initially parts of basket trials testing the same regimen in multiple cancer types. The HCC cohorts were selected for further development because of the promising antitumor activity demonstrated by these regimens, with ORRs of 10–50% and median PFS of more than 6 months (Table 1). It was recently announced that the combination of atezolizumab and bevacizumab demonstrated superior OS and PFS compared to sorafenib in the first-line treatment of advanced HCC. Randomised phase III trials comparing this type of combination regimens with the current standard of care in different settings are ongoing (Table 2).

Another promising regimen is the combination of anti-PD-1/anti-PD-L1 with anti-CTLA4 agents. Nivolumab plus ipilimumab is the most extensively studied combination immunotherapy. ORRs of 40–60% have consistently been seen in patients with advanced melanoma, non-small cell lung cancer, and RCC, and this regimen has been approved as first-line therapy for advanced RCC because it confers superior OS and ORR compared to sunitinib. Different dosing regimens of nivolumab and ipilimumab were developed in different cancer types, with grade 3–4 treatment-related adverse events more frequently (30% to 60%) observed with combination regimens than with single-agents, especially in patients who received higher dosages of ipilimumab. Fortunately, the adverse events were largely manageable by early recognition, steroid treatment, and discontinuation of immunotherapy as clinically required, and the therapeutic benefit appeared not to be affected by treatment discontinuation.

Nivolumab plus ipilimumab has been tested in patients with advanced HCC who had progressive disease after sorafenib treatment or who were intolerant to sorafenib. Patients were randomised to 3 different dosing regimens of nivolumab and ipilimumab (Table 1). The overall ORR was 31.1% (7 complete and 39 partial responders among 148 evaluable patients) and the median duration of response was 17.48 months (95% CI 11.07 to not reached). The safety profile was similar to those in other cancer types, with grade 3–4 treatment-related adverse events occurring in 55 (37.7%) patients, and 13 (8.9%) patients discontinuing study treatment due to treatment-related adverse events.

The combination of tremelimumab and the anti-PD-L1 antibody durvalumab led to an ORR of 15% in patients with advanced HCC progressing after, or intolerant to, sorafenib treatment (Table 1). A randomised trial comparing durvalumab plus tremelimumab, durvalumab monotherapy, and sorafenib as first-line therapy for advanced HCC is ongoing (Table 2).

Lessons from immuno-oncology combination trials in other cancer types

Whereas anti-PD-1/anti-PD-L1 agents remain the mainstay of immuno-oncology combination development, in recent years, there has been remarkable growth in the global immuno-oncology pipeline with more and more drug candidates targeting both adaptive and innate immunity, to the point that collaboration among multiple pharmaceutical companies is mandated. Numerous possible combinations have prompted the development of novel trial concepts that may facilitate exploitation of valuable information from limited studies.

Choice of candidate regimens based on early-phase trial results

Based on the huge promise of immuno-oncology combination regimens, it is critical to identify the optimal surrogate endpoints in early-phase clinical trials to better select the right regimens for confirmatory randomised trials.
Development and approval of single-agent ICIs relied heavily on the US FDA accelerated approval process, with ORR used as the primary efficacy endpoint in all of the ICI single-arm studies that led to accelerated approval. However, a systemic review of the single-arm and randomised trials of single-agent ICI therapy (87 and 20 trials, respectively) revealed that ORR was poorly correlated with both PFS and OS (r correlation coefficients of ORR with 6-month PFS and with 12-month OS were 0.37 and 0.08, respectively). On the other hand, a good correlation between 6-month PFS and 12-month OS was found (r correlation coefficient 0.74; 95% CI 0.57–0.92). Therefore, in single-arm trials, milestone analysis using PFS rate at specific time points may be considered a better surrogate efficacy endpoint than ORR, although larger sample sizes and longer follow-up will still be needed.

Statistical considerations
Most pivotal immuno-oncology trials tested multiple primary endpoints to capture signals of treatment efficacy as comprehensively as possible. Stringent control of the overall type I error rate in such trials is required, and many multiple testing methods, such as the gatekeeping procedures to test hierarchically ordered hypotheses and the graphical approach to recycle x across hypothesis families, have been applied to address this issue. However, the generally acknowledged clinical benefit of ICI in patients with advanced cancer may fail to reach ‘statistical significance’ with this rigorous approach, as demonstrated by the IMvigor211 trial of atezolizumab in urothelial carcinoma and the KEYNOTE-240 trial of pembrolizumab in HCC. Adjustment for post-randomisation confounding factors, such as the choice of active control, the potential difference in adherence, effects of cross-over and post-progression therapy, should also be considered. Researchers designing future clinical trials must plan more carefully for multiple primary endpoints, interim analyses, and adjustment for post-progression therapy.

The importance of predictive biomarkers
The most extensively studied predictive biomarkers for efficacy of ICI therapy are tumour mutational burden (TMB) and PD-L1 expression. High TMB, measured by whole-exome sequencing or multigene cancer panels, can predict efficacy of ICI therapy in multiple cancer types. The relative predictive value of TMB and other biomarkers, such as microsatellite instability and PD-L1 expression, may differ among different cancers and types of ICI therapy (anti-PD-1/anti-PD-L1, anti-CTLA4, or combination therapy). Many unresolved issues need to be explored in future clinical trials, including the relationship between TMB and specific genetic changes in cancer cells, the quality (immunogenicity) of the neo-antigens produced by these mutations, and the optimal predictive threshold of TMB in different cancer types. In HCC, the percentage of patients with high TMB or microsatellite instability was low, and the TMB was not correlated with the rate of predicted neo-antigens or expression patterns of immune-
related genes in the HCC microenvironment.\(^{50}\) TMB was not reported in the subsequent biomarker analysis in patients with HCC treated with either nivolumab or pembrolizumab.\(^{11,51}\) Therefore, the value of TMB as a predictive marker for efficacy of ICI therapy in HCC is unclear.

PD-L1 expression on tumour cells or immune cells has been used widely as a selective marker for immuno-oncology trial enrolment, pre-defined sub-group analysis, or as a stratification factor for randomisation in various cancer types.\(^ {52,53}\) PD-L1 expression in tumour cells, with a cut-off of \(\geq 1\%\), occurred in about 20\% of patients with HCC and might be associated with poor prognosis.\(^ {54}\) Pre-clinical models suggested that PD-L1 expression in HCC tumour cells may inhibit T cell function in the liver tumour microenvironment.\(^ {55}\) In a post hoc analysis of 195 patients with HCC treated with nivolumab in the CheckMate-40 trial, ORRs for those with PD-L1 \(\geq 1\%\) vs. <1\% were 27.7\% vs. 15.7\%, respectively. OS for those with PD-L1 \(\geq 1\%\) vs. <1\% were 28.1 months vs. 16.6 months, respectively \((p = 0.032)\).\(^ {56}\) A similar trend has been shown in a smaller cohort of patients with HCC treated with pembrolizumab (the KEYNOTE-224 trial).\(^ {11}\) These results suggest that PD-L1 expression, as a continuous variable, is a useful predictive marker, but cannot be a binary marker to help decide which patients should receive anti-PD-1 therapy.

In the era of immuno-oncology-based combination therapies, a more comprehensive approach to biomarker research is needed to characterise the complex interactions of immune regulatory networks in the tumour microenvironment and the impact of individual agents with different immunomodulatory actions.\(^ {22,56–58}\) Transcriptional analysis to measure the quantity, proportions, and functional status of immune cells, as well as inflammation as a whole, in the tumour microenvironment has rapidly advanced and may correlate with response to immuno-oncology therapy.\(^ {57,59–62}\). In HCC and other virus-associated cancers, recent studies have suggested that there might be an association between chronic viral infection and a more immune-suppressive microenvironment.\(^ {63,64}\) The definition of the immune-suppressive phenotypes and the association between these phenotypes and the efficacy of ICI therapy are being actively explored. In patients with HCC who were enrolled into the CheckMate-040 nivolumab trial and had adequate tissue for analysis \((n = 37)\), increased inflammatory signatures, as measured by different algorithms, were found to correlate with improved response and OS.\(^ {55}\) Further studies to overcome the challenge of tissue availability and quality are needed. As our understanding of the functional status of T cells, particularly exhausted T cell phenotypes, in tumour-infiltrating lymphocytes and peripheral blood from patients with HCC rapidly evolves, the predictive value of biomarkers from peripheral blood should be explored, as these biomarkers may overcome limitations of sample availability.\(^ {65–67}\)

The availability of pre- and post-treatment tumour samples during ICI therapy is crucial for biomarker research in HCC. There is an ongoing clinical trial of pembrolizumab, in which serial tumour biopsies are planned at baseline and after 2 cycles of treatment \((NCT03419481)\). In this study, single-cell sequencing of RNA will be

### Table 2. Summary of phase III trials of combination immunotherapy.

<table>
<thead>
<tr>
<th>Target population</th>
<th>Estimated patient no.</th>
<th>Regimen</th>
<th>Primary endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior systemic therapy for HCC; BCLC stage C or stage B not eligible for locoregional therapy; Child-Pugh class A</td>
<td>Clinical/histological diagnosis 480</td>
<td>Atezolizumab 1,200 mg + bevacizumab 15 mg/kg every 3 weeks vs. sorafenib</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>Clinical/histological diagnosis</td>
<td>Clinical/histological diagnosis 640</td>
<td>Atezolizumab 1,200 mg every 3 weeks + cabozantinib 40 mg/day vs. sorafenib</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>Clinical/histological diagnosis</td>
<td>Clinical/histological diagnosis 750</td>
<td>Pembrolizumab 200 mg every 3 weeks + lenvatinib (12 or 8 mg/day based on body weight) vs. lenvatinib</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>Histological/cytological diagnosis</td>
<td>Histological diagnosis 510</td>
<td>SHR-1210 200 mg every 2 weeks + atipinib 250 mg/day vs. sorafenib</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>Histological diagnosis</td>
<td>Histological diagnosis 1,310</td>
<td>Durvalumab vs. Durvalumab + tremelimumab vs. sorafenib</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>Histological diagnosis</td>
<td>Histological diagnosis 1,084</td>
<td>Nivolumab + ipilimumab vs. sorafenib or lenvatinib</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>HCC not amenable to curative treatment (surgery, transplantation, or ablation therapy) but amenable to TACE; Child-Pugh class A to B7</td>
<td>Histological diagnosis 888</td>
<td>Durvalumab vs. Durvalumab + bevacizumab vs. placebo</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>Disease-free after curative hepatic resection or ablation with high risk of recurrence</td>
<td>Histological diagnosis 642</td>
<td>Atezolizumab + bevacizumab vs. active surveillance</td>
<td>OS, PFS</td>
</tr>
</tbody>
</table>

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; PFS, progression-free survival; OS, overall survival; RFS, recurrence-free survival; TACE, transarterial chemoembolisation.
conducted on biopsy samples taken at the core and the edge of tumour, to see if changes in RNA expression of an immune-related gene panel correlate with radiological responses and survival outcomes. The results of this study will help identify potential biomarkers for prediction of responses and resistance. Obtaining pre- and post-treatment tumour samples in the setting of neoadjuvant ICI therapy is another promising possibility. Neoadjuvant anti-PD-1 therapy has shown promising antitumour activity in non-small cell lung cancer, melanoma, and glioblastoma. The most notable findings included: i) major pathological responses (no more than 10% viable tumour cells on histological examination) were almost always more frequent than clinical responses, evaluated by imaging criteria after only 1 to 2 doses of treatment; ii) increased infiltration of immune cells developed quickly, usually within 3 weeks, after treatment and was associated with significantly better ORR and survival. Preliminary reports of neoadjuvant therapy with nivolumab or nivolumab plus ipilimumab in HCC also demonstrated prominent antitumour activity with complete pathological responses in about 30% of patients, suggesting that the neoadjuvant approach is feasible and may dramatically change the role of systemic therapy in HCC.

Promise and challenges of immuno-oncology-based combination therapy for HCC
Choosing the right antiangiogenic agents for immuno-oncology combination: MKIs vs. specific VEGF/VEGFR inhibitors
While the vascular endothelial growth factor receptor (VEGFR) signalling pathway is the most extensively studied mechanism for the immunomodulatory effects of antiangiogenics, pre-clinical models have demonstrated other ‘off-target’ effects of the multikinase inhibitors (MKIs) that may contribute to antitumour immunity. Pre-clinical models exploring the immunomodulatory effects of targeted agents have been criticised for several reasons, including the comparability of the murine and the human immune system, difficulty simulating the human tumour microenvironment, and the clinical relevance of the dosage of the targeted agents used in pre-clinical models. Most researchers tended to use the ‘maximally tolerated’ dosage for mice, which may produce much higher drug exposure in mice, compared with the levels achievable in humans. A possible caveat of using MKIs is the potentially higher incidence of adverse events. In the past when targeted agents were incorporated into combination regimens, fewer than 50% of them could be given as single-agent therapy at the full recommended dosage. Treatment discontinuation due to adverse events led to discontinuation of development of some ICI-antiangiogenic combinations. In addition, rare but life-threatening adverse events, such as cardiotoxicity, may be associated with the ICI-antiangiogenic combinations.

Two critical issues must be addressed to clarify the role of MKIs in immuno-oncology combination therapy. The first is to identify immune-related antitumour mechanisms independent of the anti-VEGFR effects of individual MKIs, and the second is to define the immunologically effective dosages of individual MKIs that improve the therapeutic window. Among the approved MKIs for HCC, the immunomodulatory effects of sorafenib have been studied the most extensively. In vivo and in vitro studies demonstrated that sorafenib may enhance antitumour immunity by increasing the M1 polarisation of TAMs, enhancing CD4+ and CD8+ T cell infiltration and function suppressing Treg numbers or reversing the function of MDSCs in the tumour microenvironment. Other MKIs (lenvatinib, regorafenib, and cabozantinib) have also demonstrated antitumor immune activity in various pre-clinical models. Preclinical models of the immunomodulatory effects may be linked to the VEGF-inhibitory property of these MKIs, multiple cellular and soluble factors in the tumour microenvironment may mediate their immunomodulatory effects. Identification of the pivotal immune mediators is thus critical for more comprehensive mechanistic exploration.

The correlation between the dosage of sorafenib used in pre-clinical studies and the reported beneficial or detrimental immunomodulatory effects was recently explored by a systemic review of the published literature. Lower dosages (<30 mg/kg in vivo or <3 μM in vitro) appeared to be associated with a higher likelihood of inducing beneficial immunomodulatory effects, while higher dosages were immunosuppressive through induction of hypoxia and recruitment of MDSCs, TAMs, or other suppressive cells. Antiangiogenic agents may enhance the antitumor mechanism of antiangiogenic multikinase inhibitors versus specific VEGF/VEGFR inhibitors needs to be confirmed.

Key points
Antiangiogenic agents may enhance the antitumor immunity of immune checkpoint inhibitors. The relative benefit and antitumor mechanism of antiangiogenic multikinase inhibitors versus specific VEGF/VEGFR inhibitors needs to be confirmed.
efficacy in HCC in combination with agents targeting specific components of adaptive immunity (e.g., agonists of T cell activation or T cell exhaustion) or innate immunity (e.g., anti-CD38), agents modulating dendritic cell function (e.g., MET inhibitors) or innate immunity (e.g., anti-CD38), agents modulating dendritic cell function (e.g., MET inhibitors)103 or agents modulating the immune microenvironment (e.g., TGF-β or IDO1 inhibitors, cytokine network modulators), oncolytic viruses, cancer vaccines, and adoptive cell therapy (Fig. 2 and Table S1). The potential immunomodulatory effects of targeted agents other than antiangiogenics have also been extensively pursued. For example, inhibitors of cyclin-dependent kinases 4/6 (CDK4/6) may enhance antigen presentation, T cell infiltration and activation, and reduce suppressive cells (Tregs or MDSCs) in the tumour microenvironment. Possible mechanisms for this include senescence-induced inflammatory cytokine release and induction of an endogenous retroviral gene/double-stranded RNA response, leading to an increase in T cell recruitment and activation.104–106 Early-stage trials combining cytotoxic chemotherapy with ICI therapy are ongoing. The immunomodulatory effects of cytotoxic chemotherapy in HCC remain to be explored. Although some of the basket trials also allowed enrolment of patients with HCC, these trials generally excluded patients with chronic viral hepatitis or patients with cirrhosis and evidence of portal hypertension because of safety concerns in the early developmental stages. Even in trials with a designated HCC cohort, stringent criteria (serum HBV DNA must be undetectable or <100 IU/ml) were applied to exclude patients with active HBV infection. Therefore, the chance of detecting efficacy signals for HCC in basket trials of novel therapy is quite low.

A possible solution is to develop more relevant pre-clinical models of HCC to identify the most promising combination strategies, between anti-PD-1/anti-PD-L1 and other immune modulators, for further clinical development. Use of pre-clinical models may not only help characterise the efficacy and mechanisms of action of specific combinations, but these models may also define the optimal treatment sequence, facilitating rational clinical trial design.107 For example, the combination of anti-PD-1 and the T cell co-stimulatory receptor OX40 agonist showed antitumor synergy only when anti-OX40 was given first, followed by anti-PD-1; while simultaneous anti-PD-1 and anti-OX40 treatment may weaken the antitumor response of individual agents through induction of T cell apoptosis.108,109

**Key points**

Combinations of immune checkpoint inhibitors with other molecular targeted therapies, immune modulators, or cytotoxic agents are promising, but require further study.

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**Fig. 1. Multikinase inhibitors may modulate antitumour immunity through both angiogenesis-dependent and independent mechanisms.** Multiple immune cells may be involved in these mechanisms. The effects of sorafenib may be dose-dependent: lower dosage is more likely to induce vascular normalisation, reduce hypoxia, and improve antitumor immunity (beneficial effects). By contrast, higher dosage may paradoxically enhance hypoxia and promote immune suppression (detrimental effects)96. The dosage effects of other multikinase inhibitors (regorafenib, lenvatinib, and cabozantinib) warrant further investigation. HCC, hepatocellular carcinoma; MDSCs, myeloid-derived suppressor cells; NK cells, natural killer cells; TAM, tumour-associated macrophages; Treg, regulatory T cells.
cirrhosis and Child-Pugh score are worthy of a median of 3.4 years\(^1\) and has raised concerns on oncology agents, advanced the approval date by approval process, used for many of the immuno-(irAEs) is still evolving. The FDA’s accelerated management of immune-related adverse events in the clinic, our understanding of the manage adverse events is greatly improve the chance of success in clinical therapy.

This kind of mechanistic understanding will greatly improve the chance of success in clinical development of specific combination regimens.

Optimal management of immune-related adverse events

With the widespread use of immuno-oncology agents in the clinic, our understanding of the management of immune-related adverse events (irAEs) is still evolving. The FDA’s accelerated approval process, used for many of the immuno-oncology agents, advanced the approval date by a median of 3.4 years\(^1\)\(^\text{10}\) and has raised concerns about safety evaluation. Compared with cytotoxic and molecular targeted agents, the possibility of identifying clinically relevant toxicity of immuno-oncology agents in early-phase trials is relatively low (43% vs. 70%).\(^1\)\(^\text{11}\)\(^\text{12}\) In addition, irAEs may develop months after the start of ICI therapy, long after the typical period of safety evaluation in early-phase oncology trials (1 to 2 months), and the small sample size of these trials may not detect rare but life-threatening toxicity. Therefore, current management guidelines for irAEs are based heavily on systematic reviews of observational data, consensus guidelines, case series, and case reports. Post-marketing pharmacovigilance studies are critical to improve our understanding of irAEs.\(^1\)\(^\text{13}\)\(^\text{14}\) The impact of liver cirrhosis and Child-Pugh score are worthy of extensive investigation in HCC, as results from early-phase clinical trials implied that patients with HCC may have increased liver-related adverse events, compared with other cancer types, when treated with ICI-based combinations.\(^2\)\(^6\)

Although steroids are the mainstay of irAE treatment, their impact on the efficacy of ICI therapy and their role in irAE prevention remain controversial.\(^1\)\(^\text{15}\)\(^\text{16}\) Firstly, most of these studies indicate that treatment of irAEs with steroids or other immunomodulatory agents may not affect ICI treatment response. Whereas a negative impact on clinical outcome was associated with higher steroid dosage or longer duration of steroid therapy, the impact may not be significant after correction for the patients’ comorbidity.\(^1\)\(^\text{17}\)\(^\text{19}\) Secondly, routine prophylaxis before cytotoxic chemotherapy may not jeopardise the beneficial effects of anti-PD-1 therapy.\(^1\)\(^\text{20}\)\(^\text{121}\) Thirdly, the association between steroid use (>10 mg prednisone equivalent per day) and inferior survival outcomes reported by retrospective studies may be biased by the fact that most (>80%) patients received steroid treatment for cancer-related symptoms or comorbidities.\(^1\)\(^\text{12}\)\(^\text{23}\)

A better understanding of the mechanistic interaction between antitumor immunity and irAEs will not only improve the management of irAEs but also facilitate development of ICI regimens with a better therapeutic index.\(^1\)\(^\text{24}\) (Fig. 3). Retrospective observation of better antitumor effects in patients who develop irAEs indicated common mechanisms between induction of antitumor immunity and autoimmune reactions.\(^1\)\(^\text{17}\)\(^\text{18}\)\(^\text{125}\)\(^\text{126}\) Induction of irAEs has been

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**Fig. 2. Immuno-oncology trials of combination regimens (anti-PD1/anti-PD-L1 as backbone) for HCC.** ([www.clinicaltrials.gov](http://www.clinicaltrials.gov), accessed on 15 August 2019). HCC, hepatocellular carcinoma; IO, immuno-oncology. MTT, multi-targeted therapy.

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**Fig. 3. Mechanistic interaction between antitumor immunity and irAEs induced by immune checkpoint inhibitor therapy.** Induction of both antitumor immunity and autoimmunity reaction may involve T cells targeting shared antigens (black circles). Induction of irAE may also involve T cells activated by self-antigens (orange circles) or by non-specific T cell-associated inflammation (green circles). The use of immune modulators or low-dose steroid regimens may not significantly compromise the antitumor immunity induced by immune checkpoint inhibitor (indicated by the dashed lines). Development of irAE prevention and treatment strategies (indicated by the solid arrows) without jeopardising antitumor activity will be possible. irAE, immune-related adverse event.
shown to be associated with peripheral CD8+ T cell clonal expansion, reduced ratio of regulatory to effector T cells in the periphery, and autoantibodies targeting immune regulatory mechanisms, such as tumour necrosis factor-α (TNFα) and toll-like receptor signalling, suggesting involvement of both cellular and humoral immunity in the pathogenesis of irAEs.

While high-dose steroids remain the mainstay for grade 3–4 irAEs, other approaches have been investigated for the treatment or prevention of irAEs without hampering antitumor immunity. The most commonly used approach is the TNFα inhibitor infliximab for the treatment of irAEs that are unresponsive to steroid treatment. Pre-clinical models suggest that prophylactic TNFα blockade may prevent irAEs induced by the anti-PD-1/anti-CTLA4 combination, without negatively impacting on antitumor activity.

Other cytokine inhibitors, such as IL6 or IL-17 inhibitors, may also be efficacious for the treatment of steroid-unresponsive irAEs. A short-course of dexamethasone before cytotoxic chemotherapy might increase the proliferation and activation of Tregs and maintain the ratio of CD8+ to regulatory T cells in the periphery, suggesting that irAEs could be prevented by incorporating a short-course steroid treatment before ICI therapy.

Combination of ICIs with locoregional treatment for HCC
Locoregional therapy, including ablation therapy, transarterial chemoembolisation (TACE), internal or external radiation therapy, and hepatic arterial infusion chemotherapy, is widely used for HCC management. These treatment modalities may induce ‘immunogenic cell death’ by releasing tumour antigens from dying cancer cells and eliciting damage-associated molecular patterns, such as calreticulin and ATP release and type I interferon response, to facilitate antitumor immunity. Combinations of ICIs and locoregional therapies may further augment antitumor immunity without overlapping toxicity – preliminary data from single-arm studies support the feasibility of this approach.

The greatest challenge of this combination approach lies in the clinical trial design. The heterogeneous treatment patterns of locoregional therapy among different regions have long been considered a major hurdle for the design and conduct of international, multicentre trials of locoregional therapy in HCC, and efforts to accommodate such regional heterogeneity in HCC practice guidelines are under way. The optimal regimens of locoregional therapy (e.g., dose/fraction of radiation therapy, types of chemotherapeutic agents) that will best induce ‘immunogenic cell death’, and the timing and sequence of combined locoregional and ICI therapy should also be addressed in these trials. Most of the previous randomised clinical trials that tested the combination of systemic therapy and locoregional therapy for HCC, either concurrent or sequential, failed to demonstrate a survival benefit of combination therapy. The post-randomisation confounding factors previously mentioned contributed greatly to the failure of these trials. About 10 to 20% of patients randomised to the locoregional therapy arm of the clinical trials could not receive the assigned treatment because of technical difficulties. The differences in adherence to study treatment (e.g., scheduled vs. on-demand TACE) and management of treatment-related adverse events, and imbalance of cross-over also confounded the results.

Nevertheless, many of these studies revealed a trend of improved ORR or PFS in patients who underwent combination therapy, suggesting that trial design using multiple primary endpoints, as discussed above, may better delineate the efficacy of combination therapy and should be considered in future clinical trials.

Conclusions
Anti-PD-1/anti-PD-L1 based combination therapy is expected to revolutionise the landscape of systemic therapy for HCC. Prioritising different combination regimens will depend on our understanding of the actual immunomodulatory mechanisms in the various combinations, the availability and validity of predictive biomarkers, and the optimal prevention and management of irAEs. The design of clinical trials from early-phase exploration to pivotal confirmatory trials is rapidly evolving and lessons from different cancer types may broaden our perspective on the new drug development process.

Abbreviations
AE, adverse event; CR, complete response; CTLA4, cytotoxic T-lymphocyte-associated protein 4; DoR, duration of response; mRECIST, modified RECIST; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; MDSCs, myeloid-derived suppressor cells; MKIs, multikinase inhibitors; NK cells, natural killer cells; NSCLC, non-small cell lung cancer; ORR, objective response rates; OS, overall survival; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PR, partial response; RCC, renal cell carcinoma; TACE, transarterial chemoembolisation; TAMs, tumour-associated macrophages; TMB, tumour mutational burden; TNFα, tumour necrosis factor-α; Tregs, regulatory T cells; VEGFR, vascular endothelial growth factor receptor.

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Conflict of interest
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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors’ contributions
All authors conceived the structure of this review. Dr. Ann-Lii Cheng and Dr. Chiun Hsu collected the data and drafted the manuscript. All authors revised the manuscript and approved the final version.

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