EDITORIAL

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Hepatocellular carcinoma and immune therapy from a clinical perspective: where are we?

“The next few years will likely see the evaluation in the clinic of new immune-based combinations...”

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The incidence of hepatocellular carcinoma (HCC) has been reported to continue to increase in the past decades [1], however, we and other groups have found that this might be changing in the USA [2,3]. In our study – based on SEER data – there seemed to be a plateau in incidence rate around 2007, and that the rate of diagnosis in patients with smaller tumors (<5 cm) surpassed larger tumors around 2005. Despite these positive findings, less than 25% of patients received potentially curative treatment with liver transplantation, resection or ablation. In patients who are not candidates for curative treatments, options are limited to transcatheter arterial chemoembolization (TACE) for intermediate stage disease and, in the advanced disease setting, systemic therapy with sorafenib, the only US FDA-approved drug treatment [4,5]. Recently, a Phase III trial reported that regorafenib in the second-line setting improved overall survival by 2.8 months

(10.6 vs 7.8 months) when compared with placebo (HR: 0.62; $p < 0.02$) [6]. This was the first positive trial in many years and we will await further details from this study. There have been several Phase II and III trials attempting to improve the limited treatment options in HCC but unfortunately these trials have been negative [7]. Other Phase III trials that are ongoing in second-line setting include cabozantinib (NCT01908426), MET inhibitor tivantinib (NCT01755767) and the VEGFR2 inhibitor ramucirumab (NCT02435433). Thus there is an urgent need to find alternative durable and well-tolerated treatments in HCC.

There are many indications in the literature suggesting that HCC should be amenable to immune therapy. HCC has been reported to a cancer type where spontaneous tumor regressions are seen [8], although this is likely due to diverse mechanisms including either immune responses or vascular

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• check point inhibitors • CTLA-4 inhibitor • hepatocellular carcinoma • immune therapy • PD-1 inhibitor • radiofrequency ablation • RFA • TACE • transcatheter arterial chemoembolization

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auto-embolization by tumor [9]. HCC is characterized by chronic inflammation and immune inhibitory checkpoints appear to be contributing to immune suppression in this setting [10] and subsequently the development and progression of HCC [11,12]. The liver is unique in the required intricate balance it needs to strike between not over-reacting to the antigens absorbed by the gut and accurate immune responses and elimination of tumor antigen. Tregs and myeloid-derived suppressor cells are thought to be important in protecting the tumor from eradication by activated cytotoxic CD8⁺ T cells. High levels of Tregs in tumor have been linked to poor prognosis in HCC. There are many excellent reviews describing these multifaceted immune interactions in detail [7,12]. Therapeutically, blockade of the so-called immune checkpoints will only work in the setting of an ongoing antitumor immune response. In patients with advanced HCC and concurrent hepatitis C virus, a Phase II trial evaluated tremelimumab, a CTLA-4 inhibitor. The trial showed partial response rate of 17.6%, stable disease 76.4% and time to progression was 6.5 months, providing proof of principle that alleviating the suppression of antitumor immunity can be effective at least in a subset of patients. Interestingly, a decrease in viral load was observed, presumably due to enhanced T-cell response [13]. With regard to the other major 'checkpoint', PD-1, promising interim data for nivolumab was reported at the annual ASCO meeting 2016 by El-Khoueiry *et al.* [14]; at the time of analysis 48 patients were evaluable for response, with an objective response rate of 15%, including 3 patients with complete response and 50% with stable disease, with median overall survival of 15.1 months, an impressive result for the second-line setting. Notably, response did not appear to be related to PD-L1 expression or hepatitis infection status. The treatment was tolerable and in a subset of patients the clinical benefit was durable. To further optimize outcome, combination strategies are needed to overcome tumor

evasion. The combination of anti-CTLA 4 and anti PD-1 dual blockade was FDA approved in September 2015 in melanoma [15]. In view of the early data seen in HCC with single-agent checkpoint inhibitor, combination therapy appears the logical next step, and this is currently underway in the clinic (NCT02519348). What about other strategies? One of the great potentials of immune modulating therapies is that they can dovetail with standard modalities, enhancing their effects on the immune system. For example, both TACE and radiofrequency ablation (RFA) have been shown to stimulate systemic antitumor immunity, presumably from release of tumor antigen [16–19] and hold promise for combining with immune modulation. Indeed, this approach has been shown to be safe, feasible and associated with encouraging clinical activity in an advanced patient population [20]. Most of the trials underway are in advanced HCC second-line setting, but there is also a Phase III study ongoing comparing nivolumab with sorafenib as first-line therapy in advanced HCC, the aim is to enroll 726 patients (NCT02576509). This is an exciting time for immune-based approaches in HCC and the early data suggest that a subset of patients are benefiting, with durable responses, and good tolerability, in a disease with few treatment options beyond local therapies. The next few years will likely see the evaluation in the clinic of new immune-based combinations, either paired with each other or with standard treatment modalities, enhancing and magnifying their effects.

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