Promising anticancer therapy: combination of immune checkpoint inhibitors and molecular-targeted agents

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Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer death worldwide, and prognosis remains unsatisfactory when the disease is diagnosed at an advanced stage. Sorafenib resistance is one of the main obstacles to the treatment of advanced HCC. Several studies have proposed that the activation of escape pathways from RAF/MEK/ERK/STAT3 might result in sorafenib resistance (1-3). Leung et al. showed that HCC cells with higher SHP2 expression was associated with a lower sensitivity towards sorafenib treatment (4). Consistently, SHP2 inhibitor SHP099 abrogated sorafenib resistance in cancer cells by blocking RAS/MEK/ERK and AKT signaling pathways (4). Unlike other tyrosine phosphatases, SHP2 functions as a positive regulator of proliferative signals. SHP2 is involved in RTK signaling, including EGFR, VEGFR, PDGFR, and EGFR signaling and activates RAS/MEK/ERK and PI3K/AKT/mTOR pathways (4,5). SHP2 transcript levels was upregulated in HBX-transfected HCC cells via NF-κB activation (6). NF-κB might directly upregulate the expression of SHP2 (4). Therefore, similar to NF-κB (7-9), SHP would regulate immune response and cancer biology in a conditional- and cell type-dependent manner.

The immune systems are controlled in healthy individuals by a range of negative regulatory signals and checkpoints. SHP-2 is involved in immune response and cancer biology in a conditional- and cell type-dependent manner. In T-cells, SHP-1 and -2 are negative regulators of antigen-dependent activation and proliferation. SHP-2 interacts directly with PD-1 in activated T-cells (10). By blocking the PD-1 signaling, CD8 T-cells form more stable and durable synapses with antigen presenting cells (11). This leads to reduced activation thresholds and increased proliferation of immune cells. The authors found that combination treatment with SHP2 inhibitor and sorafenib led to maximal suppression of tumor growth with significantly improved survival rate (4). In addition, they found enhance T cell infiltration in both SHP2 blockade alone and combo treatment, which implicates the potential role of SHP2 inhibitor in modulation of T cells for immune cancer therapy (4). Interestingly, it has been reported that combining MEK inhibition with immune checkpoint inhibitor (ICI) resulted in synergistic and durable tumor regression even where either agent alone was only modestly effective (12). Given that SHP2 regulates MEK/ERK signaling, SHP2 would be a promising drug target in combination with ICI. Recently, it was reported that combination trial of PD-L1 antibody, atezolizumab, with anti-VEGF antibody, bevacizumab (IMbrave150 trial) was positive. Many other phase III clinical trials of a combination therapy of ICI and molecular targeted agents are ongoing (Figure 1), which suggests treatment paradigm of HCC will be changed drastically in the very near future (13-15). Combination therapy with ICI would provide new strategies in the treatment of liver cancer.
Figure 1 Ongoing Phase III trials in HCC. HCC, hepatocellular carcinoma.

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Footnote
All authors have completed the ICMJE uniform disclosure form and declare: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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