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IMMUNOTHERAPY

Nivolumab keeps HCC in check and opens avenues for checkmate

Annually, ~750,000 new cases of hepatocellular carcinoma (HCC) are diagnosed worldwide, mostly at an advanced stage, with dismal outcomes. Sorafenib, the only approved systemic therapy for advanced-stage HCC, is of limited benefit, and no standard second-line therapy exists. New data indicate the therapeutic potential of immunotherapy with the anti-PD-1 antibody nivolumab in this disease.

In the phase I/II CheckMate 040 trial, 262 patients with advanced-stage HCC were treated with nivolumab; 76% had received prior systemic therapy, predominantly with sorafenib, and 68% had extrahepatic disease. In a dose-escalation cohort comprising 48 patients, only one dose-limiting toxicity was observed, and no maximum tolerated dose was defined. Among this group, the objective response rate (ORR) was 15%, with three complete and four partial responses, and the disease control rate (DCR) was 58%. The median overall survival duration was 15 months; at both 6 and 9 months, 66% of patients were alive.

In a dose-expansion cohort, 214 patients received nivolumab at a dose of 3 mg/kg every 2 weeks. The ORR was 20%, comprising three complete and 39 partial responses, and the DCR was 64%; 6-month and 9-month survival was 83% and 74%, respectively. Of note, the ORRs were similar across groups stratified according to hepatitis B or C status, or sorafenib exposure, and were independent of PD-L1 expression level (<1% or ≥1% on tumour cells). To put these findings into perspective, the ORRs in previous trials of first-line sorafenib and second-line regorafenib were only 2–3% and ~7%, respectively. Furthermore, the median overall survival with first-line sorafenib is typically <11 months.

Importantly, nivolumab was well tolerated, irrespective of hepatitis B/C infection, with no new safety signals. In the dose-expansion cohort, 40 patients (19%) had grade 3 or 4 adverse events, nine of which were classed as 'serious', and only 24 patients discontinued treatment owing to toxicity. Moreover, EQ-5D-3L index assessments at baseline and at 25 weeks revealed no significant changes in patient-reported health-related quality of life.

> "...nivolumab therapy, in the first or second line, can keep advanced-stage HCC in check..."

Although results of randomized comparisons are needed, these findings strongly suggest that nivolumab therapy, in the first or second line, can keep advanced-stage HCC in check. In addition, the good safety profile of nivolumab provides scope to achieve 'checkmate' with combination therapies, in both advanced and early disease settings. Notably, anti-CTLA-4 antibody therapy has promising efficacy in patients with HCC, warranting investigation of dual PD-1/CTLA-4 blockade, which has proven efficacy in other cancers.

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ORIGINAL ARTICLE El-Khoueiry, A. B. *et al.* Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* http://dx.doi.org/10.1016/S0140-6736(17)31046-2 (2017)