INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Clinical Benefits of Immune Checkpoint Inhibitors and Predictive Value of Tumor Mutation Burden in Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

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Review question / Objective: **Is immunotherapy associated with beneficial clinical outcomes for hepatocellular carcinoma (HCC) and how can combination immunotherapy be deployed to produce the best benefit? Is tumor mutation burden (TMB) a predictive biomarker for immune-checkpoint inhibitors?**
Condition being studied: **To this date, about 50 single-arm clinical trials and several randomized control trials (RCTs) presented final or interim results of investigations on the efficacy of PD-1/PD-L1 inhibitors for advanced HCC. In the CheckMate 459, IMbrave 050, and ORIENT-32, immunotherapies were found to significantly improve progression-free survival (PFS) and overall survival (OS) compared with sorafenib (a tyrosine-kinase inhibitor, as standard systemic treatment) in patients with advanced hepatocellular carcinoma. However, these clinical trials were different on clinical phases, sample size, and response evaluation criteria, and inconsistent clinical outcomes were shown in several trials.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 January 2022 and was last updated on 02 January 2022 (registration number INPLASY202210008).

INTRODUCTION

Review question / Objective: **Is immunotherapy associated with beneficial clinical outcomes for hepatocellular carcinoma (HCC) and how can combination immunotherapy be deployed to produce the best benefit? Is tumor mutation burden (TMB) a predictive biomarker for immune-checkpoint inhibitors?**

Rationale: The beneficial role of immunotherapy and clinical relevance of tumor mutation burden (TMB) in hepatocellular carcinoma remain inconclusive; thus, combination immunotherapy and reliable predictor need to be determined to guide suitable strategies. To evaluate the association of clinical outcomes with PD-1/PD-L1 inhibitors in patients with advanced hepatocellular carcinoma and to explore appropriate strategies and evaluate the predictive performance of TMB.

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METHODS

Search strategy: The following terms were used to define the disease: hepatocellular carcinoma, HCC, liver cancer, and liver cell carcinoma. We searched for clinical trials using the specific terms: immunotherapy, immune checkpoint inhibitor, programmed death-ligand 1, programmed death receptor 1, tumor mutational burden,nivolumab, opdivo, pembrolizumab, keytruda, atezolizumab, durvalumab, avelumab, camrelizumab, cemiplimab, tislelizumab, toripalimab, sintilimab, penpulimab, jemperli. In addition, we also checked all relevant articles to identify studies that reported HRs for PFS and OS according to TMB.

Participant or population: People with advanced hepatocellular carcinoma.

Intervention: PD-1/PD-L1 inhibitors.

Comparator: Sorafenib.

Study designs to be included: RCTs and single-arm trials regarding PD-1/PD-L1 antibodies for people with advance hepatocellular carcinomaHCC.

Eligibility criteria: The inclusion criteria for considering studies for this review were: (1) clinical trials including monotherapy or combination therapy of PD-1 or PD-L1 inhibitor for patients with advanced or metastatic HCC (excluded monotherapy of CTLA-4 inhibitor or real-world studies); (2) clinical trials with reported available data that measured objective response rate (ORR), disease control rate (DCR), PFS, or OS; (3) published in English; (4) sample size greater than 10; (5) the latest reported data were included for past clinical trials.

Information sources: We searched the following electronic databases (Pubmed, Embase, Cochrane Library, Web of Science, and clinicaltrials.gov) and the meeting abstracts of conferences (ASCO, ESMO, AACR) from inception to 31st December 2021 for all anti-PD-1 or anti-PD-L1 monotherapies and combination therapies.

Main outcome(s): Overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).

Additional outcome(s): HRs of progression-free survival (PFS) and overall survival (OS) for TMB-H vs TMB-L groups.

Quality assessment / Risk of bias analysis: The study quality assessment tools developed by NHLBI (National Heart, Lung, and Blood Institute, https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) was used to determine the quality of included studies.

Strategy of data synthesis: Meta-analysis was performed using a random-effects model (DerSimonian and Laird method).

Subgroup analysis: In subgroup analysis, studies were divided into groups according to the treatment strategies and the combined effects between the groups were compared. The differences in treatment effect between subgroups were measured by P value for interaction.

Sensitivity analysis: Egger's test was performed to evaluate publication bias.

Language: Published in English.

Country(ies) involved: China.

Keywords: hepatocellular carcinoma; immunotherapy; immune checkpoint inhibitor; PD-1/PD-L1; anti-VEGF; tumor mutation burden; atezolizumab; sintilimab.

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