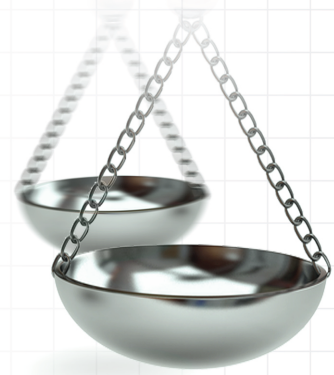
Meta-Analysis



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Network meta-analysis of nivolumab plus ipilimumab in the second-line setting for advanced hepatocellular carcinoma

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Aims: To compare the efficacy of nivolumab 1 mg/kg + ipilimumab 3 mg/kg with regorafenib 160 mg, cabozantinib 60 mg and nivolumab 3 mg/kg monotherapy for second-line treatment of advanced hepatocellular carcinoma. **Materials & methods:** Indirect comparison using network meta-analysis and propensity score weighting. **Results:** Nivolumab 1 mg/kg + ipilimumab 3 mg/kg had significantly higher objective response rate (median 31.2% [95% credible interval: 19.6–44.5%]) than cabozantinib (4.2% [2.0–6.5%]) and regorafenib (4.8% [1.1–8.3%]), and significantly longer overall survival (cabozantinib: hazard ratio: 0.46 [95% credible interval: 0.27–0.79]; regorafenib: 0.56 [0.32–0.97]). Nivolumab 1 mg/kg + ipilimumab 3 mg/kg had significantly better objective response rate (difference 21.0% [4.5–37.5%]) and overall survival (hazard ratio: 0.58 [0.35–0.96]) than nivolumab monotherapy. **Conclusion:** Nivolumab 1 mg/kg + ipilimumab 3 mg/kg had a superior efficacy versus cabozantinib 60 mg, regorafenib 160 mg and nivolumab 3 mg/kg monotherapy as second-line therapy for advanced hepatocellular carcinoma.

Tweetable abstract: Indirect comparisons found nivolumab 1 mg/kg + ipilimumab 3 mg/kg had a superior objective response rate and overall survival versus cabozantinib 60 mg, regorafenib 160 mg and nivolumab 3 mg/kg monotherapy as second-line therapy for patients with advanced hepatocellular carcinoma.

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Keywords: advanced hepatocellular carcinoma • immunotherapy • network meta-analysis • nivolumab and ipilimumab combination therapy • objective response rate • overall survival • second-line treatment

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the fourth most common cause of cancer-related death worldwide, accounting for 75–85% of all liver cancers [1]. In the US, the incidence rate of HCC is 13.5 per 100,000 person-years, which is projected to increase in the next two decades [2]. HCC is often advanced at the time of detection [3] based on the Barcelona Clinic Liver Cancer (BCLC) staging criteria [4]. Without treatment, the median survival for advanced HCC is only 7.9 months, and the 5-year overall survival (OS) is less than 5% [3,5]. Poor disease prognosis is predicted by Child–Pugh classification [6] and Eastern Cooperative Oncology Group (ECOG) performance status [7], elevated AFP levels, extrahepatic spread and macrovascular invasion [8]. Sorafenib is currently approved for use in the first-line setting of advanced HCC [9,10]. However, it is associated with limited objective response rates (ORRs) and considerable toxicities [5,11]. In the second-line setting, regorafenib [12] and cabozantinib [13] were approved by the US FDA for the treatment of advanced HCC on 27 April 2017 and 14 January 2019, respectively. However, these second-line treatment options have also demonstrated limited response rates ranging from 4 to 11% in clinical trials [12,13].

Recent breakthroughs in immunotherapy have yielded promising results in the treatment of advanced HCC [14–18]. The FDA approved two immune checkpoint inhibitors of PD-1, nivolumab and pembrolizumab (approved on

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22 September 2017 and 9 November 2018, respectively), as second-line treatments for HCC in patients who have previously received sorafenib [19,20]. Ramucirumab, a vascular endothelial growth factor inhibitor, was approved on 10 May 2019, for the treatment of advanced HCC in patients with elevated levels of AFP (≥400 ng/ml) [18]. In March 2020, nivolumab in combination with ipilimumab, a CTLA-4 inhibitor, was approved in the US at a dose of nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) in the second-line setting for advanced HCC [19] based on the results of the CheckMate 040 Phase I/II study [21].

The efficacy of nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W was assessed in the CheckMate 040 study, as well as nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W and nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks. CheckMate 040 was a Phase I/II study in patients with advanced HCC, yielding an ORR of 31% for the nivolumab 1 mg/kg + ipilimumab 3 mg/kg group [21]. Despite the recent FDA approval, comparative studies evaluating the efficacy of nivolumab 1 mg/kg + ipilimumab 3 mg/kg relative to other second-line treatments are currently lacking. Given the recent approval of nivolumab 1 mg/kg + ipilimumab 3 mg/kg and the urgent need for improved treatment options for advanced HCC, comparative efficacy studies are essential to informing decision-making in clinical practice. Therefore, the present study evaluated the ORR and OS in patients with advanced HCC treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg versus other second-line treatments, including cabozantinib, regorafenib and nivolumab monotherapy. The analysis was limited to the comparative efficacy of the included regimens and relative tolerability was not assessed.

Materials & methods

Study identification

We conducted a targeted literature review to identify clinical trials for treatments approved for patients with advanced HCC who have been previously treated with sorafenib. Clinical trials for treatments indicated in specific subgroups of patients with advanced HCC (e.g., ramucirumab, indicated only for patients with AFP ≥400 ng/ml [18]) were not included. A feasibility assessment was further conducted to evaluate data availability and similarities in key trial characteristics, including study population, inclusion/exclusion criteria, key baseline characteristics and definitions of outcomes of studies identified in the targeted literature review. Based on the feasibility assessment, the CheckMate 040 (NCT01658878) [22], RESORCE (NCT01774344) [12] and CELESTIAL (NCT01908426) [13] studies were included in this study.

The relative efficacy of each treatment regimen could not be compared directly because of a lack of head-to-head clinical trials. To overcome this challenge, network meta-analysis (NMA) was used to synthesize data from a network of randomized controlled trials through a common comparator [23,24]. A combination of matching-adjusted indirect comparison (MAIC) [25,26] and NMA approaches was required to assess evidence from the nonrandomized, uncontrolled CheckMate 040 study. Finally, the efficacy of nivolumab 1 mg/kg + ipilimumab 3 mg/kg versus nivolumab monotherapy was compared using propensity score weighting to control for differences in baseline characteristics between the two groups.

MAIC & NMA

The trials for regorafenib 160 mg (RESORCE) and cabozantinib 60 mg (CELESTIAL) were randomized, placebo-controlled trials, which could be connected via placebo in the NMA. However, the only evidence available for nivolumab 1 mg/kg + ipilimumab 3 mg/kg in advanced HCC was the nonrandomized, cohort-based CheckMate 040 study. Therefore, we used a combination of MAIC and NMA approaches to indirectly compare cabozantinib 60 mg, regorafenib 160 mg and nivolumab 1 mg/kg + ipilimumab 3 mg/kg through a common comparator (i.e., placebo). Published aggregated data were used for cabozantinib 60 mg and regorafenib 160 mg and their placebo arms. Nivolumab 1 mg/kg + ipilimumab 3 mg/kg was connected to the evidence network through its association with placebo established in the MAIC analysis.

There were some key differences among the patient populations in the three trials, which might have impacted the outcomes [12,13,21]. In CheckMate 040, participants were previously treated with sorafenib and were permitted to have received multiple lines of prior therapy. CELESTIAL accepted patients starting second- or third-line treatments, whereas RESORCE only accepted patients in the second-line setting. In CheckMate 040, participants had previously progressed on or been intolerant to sorafenib treatment. In CELESTIAL, patients had prior sorafenib treatment and progression after at least one systemic therapy. In RESORCE, participants progressed on prior sorafenib treatment.

Table 1. Baseline characteristics before and after matching-adjusted indirect comparison.

Baseline characteristics (%)	Before matching			After matching	
	NIVO 1 mg/kg + IPI 3 mg/kg (n = 50)	Placebo (n = 237)	p-value	NIVO 1 mg/kg + IPI 3 mg/kg	Placebo
Age ≥65 (years)	38.0	47.7	0.27	47.7	47.7
Male	86.0	85.2	1.00	85.2	85.2
BCLC stage					
– 0	2.0	0.0	0.17	0.0	0.0
– A	4.0	0.0	<0.05†	0.0	0.0
– B	8.0	9.7	1.00	9.7	9.7
– C	86.0	90.3	0.52	90.3	90.3
ECOG performance status					
– 0	62.0	55.3	0.47	55.3	55.3
– 1	38.0	44.7	0.47	44.7	44.7
AFP level					
– ≥400 ng/ml	50.0	42.6	0.42	42.6	42.6
– <400 ng/ml	50.0	57.4	0.42	57.4	57.4
Prior treatments (n)					
– 1	70.0	73.4	0.75	73.4	73.4
– 2	22.0	26.2	0.66	26.2	26.2
– >2	8.0	0.4	<0.01†	0.4	0.4

†Indicates a significant difference with a p-value <0.05.
BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group; IPI: Ipilimumab; NIVO: Nivolumab.

The MAIC established the comparative efficacy between nivolumab 1 mg/kg + ipilimumab 3 mg/kg and placebo in the CELESTIAL study. This placebo arm was selected because of the similarities in study design and key baseline characteristics compared with the nivolumab 1 mg/kg + ipilimumab 3 mg/kg arm in the CheckMate 040 study, as described above. Patients who were treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg in the CheckMate 040 study were weighted so that the distribution of key patient characteristics (including age, sex, BCLC stage, ECOG performance status, AFP level and number of prior treatments) matched that of the placebo arm from the CELESTIAL study (Table 1) [25,26]. Variables were selected based on the prognostic value of the variable, data availability and observed differences in the distribution among treatment groups.

The main outcomes for the MAIC were ORR and OS. ORRs were based on local investigator assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [27]. To compare the OS assessed by hazard ratios (HRs), pseudo patient-level OS data for the placebo arm of the CELESTIAL study were estimated based on the published Kaplan–Meier curve using the Guyot algorithm [28].

After the MAIC analysis, separate NMAs were conducted to assess the ORR and HR of OS. Specifically, the ORR was assessed using additive NMA models instead of odds ratio models to avoid unstable estimations when the ORR was close to zero. The HR of OS comparing treatments of interest with placebo was modeled on the multiplicative scale. All models were based on a Bayesian approach using the Markov chain Monte Carlo method with a noninformative prior to estimate the probability distribution for each parameter of interest [29]. Fixed-effect models were chosen given the small size of the network and the mild heterogeneity among the studies. The distribution for absolute measures (ORR) and relative measures (HR of OS and difference in ORR) were summarized using posterior medians and associated 95% credible intervals (CrIs). Data input for the NMA are summarized in Table 2.

Propensity score weighting

Additionally, ORR and OS were compared between nivolumab 1 mg/kg + ipilimumab 3 mg/kg and nivolumab 3 mg/kg monotherapy via a propensity score weighted analysis using patient-level data from the CheckMate 040 study. Before weighting, 204 patients were included in the comparison: 50 in the nivolumab 1 mg/kg + ipilimumab 3 mg/kg group and 154 in the nivolumab 3 mg/kg monotherapy group. After weighting, 13 patients with missing data in the matched covariates (eight missing age and five missing AFP level) were excluded, leaving 191 patients

Table 2. Trial data included in the network meta-analysis.

Study	Treatment	Number analyzed	Investigator-assessed ORR, %	HR vs placebo (95% CI)
MAIC (CheckMate 040 vs CELESTIAL)	NIVO 1 mg/kg + IPI 3 mg/kg	50	30.4	0.35
	Placebo (CELESTIAL)	237	0.4	(0.21–0.58)
CELESTIAL	Cabozantinib 60 mg	470	3.8	0.76
	Placebo	237	0.4	(0.63–0.92)
RESORCE	Regorafenib 160 mg	379	6.6	0.63
	Placebo	194	2.6	(0.50–0.79)

HR: Hazard ratio; IPI: Ipilimumab; MAIC: Matching-adjusted indirect comparison; NIVO: Nivolumab; ORR: Objective response rate.

Table 3. Baseline characteristics before and after propensity score weighting.

Baseline characteristics	Before weighting			After weighting†		
	NIVO 3 mg/kg (n = 154)	NIVO 1 mg/kg + IPI 3 mg/kg (n = 50)	p-value	NIVO 3 mg/kg	NIVO 1 mg/kg + IPI 3 mg/kg	p-value
Age, mean (SD), years	61.5 (12.2)	59.5 (12.1)	0.21	60.8 (12.6)	60.6 (10.9)	0.91
Race (%)			0.02‡			0.95
– White	46.1	24.0		37.0	35.9	
– Asian	51.9	74.0		61.1	61.3	
– Other	1.9	2.0		1.9	2.8	
ECOG performance status = 1 (%)	35.1	38.0	0.84	37.8	37.8	1.00
BCLC stage (%)			0.21			0.23
– 0	0.0	2.0		0.0	1.1	
– A	1.3	4.0		1.4	4.6	
– B	9.1	8.0		10.7	7.3	
– C	89.6	86.0		87.9	86.9	
Presence of macrovascular invasion (%)§	28.6	36.0	0.42	29.1	32.8	0.67
Presence of extrahepatic spread (%)	71.4	80.0	0.31	74.4	74.7	0.97
AFP level ≥400 ng/ml (%)	38.3	50.0	0.20	42.2	42.9	0.93
≥2 prior treatments (%)	19.5	30.0	0.17	23.1	23.0	0.99
Previous radiotherapy (%)	24.0	28.0	0.71	25.4	22.6	0.70
Previous surgery (%)	66.2	72.0	0.56	70.3	75.5	0.49

†Patients with missing data in any of the above covariates were excluded after weighting (eight missing in age and five missing in AFP level).
‡Indicates a significant difference with a p-value <0.05.
§Invasion of the hepatic vein or portal vein.
BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group; HBV: Hepatitis B virus; HCV: Hepatitis C virus; IPI: Ipilimumab; NIVO: Nivolumab.

in the comparison. ORRs were evaluated based on both local investigator assessment according to RECIST v1.1 and via blinded independent central review (BICR) assessment according to RECIST v1.1. Inverse probability treatment weighting based on propensity scores was used to balance key patient characteristics (including age, race, BCLC stage, ECOG performance status, macrovascular invasion, extrahepatic spread, AFP level, number of prior treatments, previous radiotherapy and previous surgery) to control for confounding [30,31]. The propensity scores were estimated using a logistic regression with the selected covariates (Table 3). Linear regression models were used to assess the difference in ORRs comparing nivolumab 1 mg/kg + ipilimumab 3 mg/kg with nivolumab 3 mg/kg monotherapy. Survival curves were compared using log-rank testing. Cox proportional-hazard models were used to

Table 4. Network meta-analysis of objective response rate.

Treatment	ORR posterior estimate, % (95% CrI)	Difference in ORR NIVO + IPI vs comparators, % (95% CrI)
Placebo	1.0 (0.3–1.8)	30.1 (18.6–43.5)
Cabozantinib 60 mg	4.2 (2.0–6.5)	26.9 (15.2–40.4)
Regorafenib 160 mg	4.8 (1.1–8.3)	26.4 (14.3–40.1)
NIVO 1 mg/kg + IPI 3 mg/kg	31.2 (19.6–44.5)	–

CrI: Credible interval; IPI: Ipilimumab; NIVO: Nivolumab; ORR: Objective response rate.

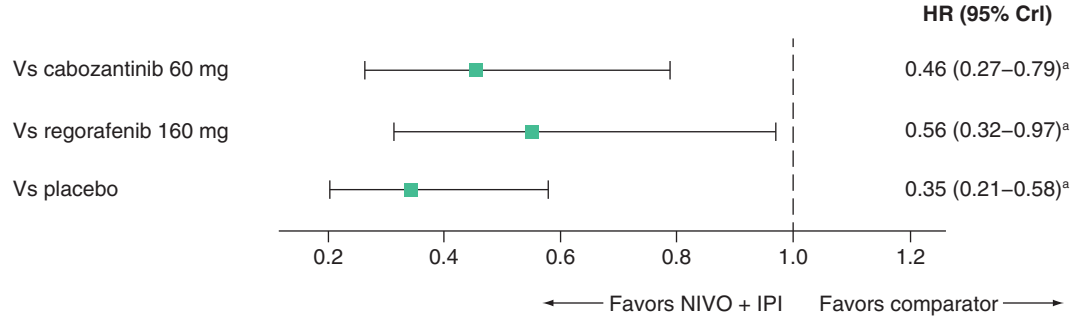

Figure 1. Network meta-analysis of hazard ratios for overall survival.
CrI: Credible interval; HR: Hazard ratio; IPI: Ipilimumab; NIVO: Nivolumab.

estimate the HR of OS. Weighted regression models with robust variance estimators were used to incorporate the propensity score weights.

All analyses were implemented using the statistical software R, OpenBUGS and Just Another Gibbs Sampler (also known as JAGS).

The present investigation was based on previously conducted studies and does not contain any procedures with human participants or animals performed by any of the authors.

Results

MAIC & NMA

We compared the baseline characteristics of patients treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg in the CheckMate 040 study and patients treated with placebo in the CELESTIAL study. Before matching, significant differences were observed between the nivolumab 1 mg/kg + ipilimumab 3 mg/kg and placebo groups in the proportion of patients with BCLC stage A (4.0 vs 0.0%; $p < 0.05$) and more than two prior treatments (8.0 vs 0.4%; $p < 0.01$). After matching, all included baseline characteristics were balanced between the two groups (Table 1).

In the MAIC analysis, the after-matching investigator-assessed ORR was 30.4% for patients treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg and 0.4% for patients treated with placebo (Table 2). The after-matching HR for OS was 0.35 (95% CI: 0.21–0.58) for nivolumab 1 mg/kg + ipilimumab 3 mg/kg compared with placebo. The after-matching results were largely similar to the before-matching results and were subsequently used in the NMA.

In the NMA, the estimated median ORR (95% CrI) of nivolumab 1 mg/kg + ipilimumab 3 mg/kg was 31.2% (19.6–44.5%), which was substantially higher than that of cabozantinib 60 mg (4.2% [2.0–6.5%]) and regorafenib 160 mg (4.8% [1.1–8.3%]; Table 4).

Nivolumab 1 mg/kg + ipilimumab 3 mg/kg also demonstrated significantly better survival outcomes, indicated by significant HRs [95% CrI] for OS compared with cabozantinib 60 mg (HR: 0.46 [0.27–0.79]) and regorafenib 160 mg (0.56 [0.32–0.97]; Figure 1).

Table 5. Comparison of objective response rate before and after propensity score weighting.

Parameters	ORR		NIVO 1 mg/kg + IPI 3 mg/kg vs NIVO 3 mg/kg	
	NIVO 3 mg/kg	NIVO 1 mg/kg + IPI 3 mg/kg	Difference in ORR, % (95% CI)	p-value
Investigator-assessed ORR				
Before weighting	20.1	32.0	11.9 (-1.5–25.3)	0.084
After weighting	19.8	30.7	10.9 (-4.3–26.2)	0.161
BICR-assessed ORR				
Before weighting	14.3	32.0	17.7 (5.5–30.0)	0.005†
After weighting	14.9	35.9	21.0 (4.5–37.5)	0.013†

†Indicates a significant difference with a p-value <0.05.
BICR: Blinded independent central review; IPI: Ipilimumab; NIVO: Nivolumab; ORR: Objective response rate.

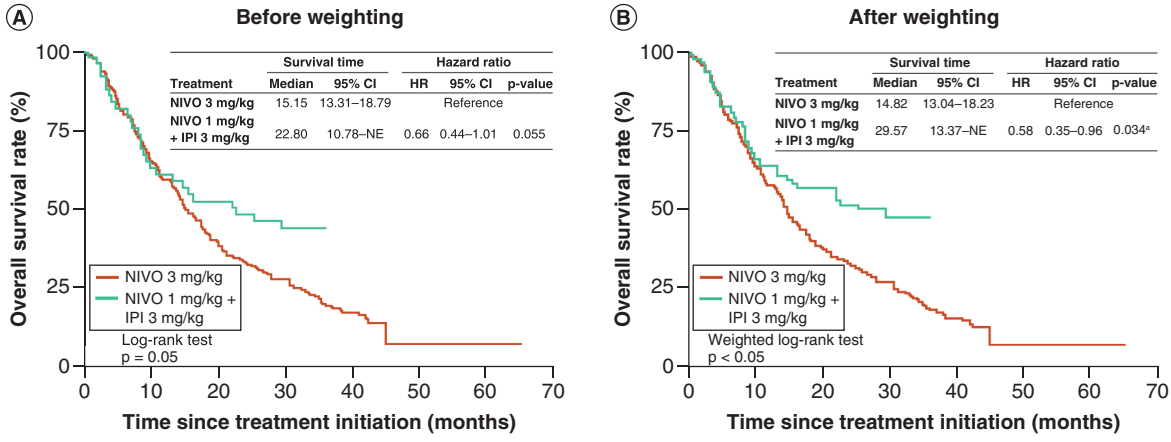

Figure 2. Kaplan–Meier analysis of overall survival. (A) Before propensity score weighting and **(B)** after propensity score weighting.
HR: Hazard ratio; IPI: Ipilimumab; NIVO: Nivolumab.

Propensity score weighting

After propensity score weighting, key baseline characteristics in the nivolumab 1 mg/kg + ipilimumab 3 mg/kg treatment group and the nivolumab 3 mg/kg monotherapy group had similar distributions in terms of the means and proportions (Table 3).

Investigator-assessed and BICR-assessed ORR values before and after weighting are presented in Table 5. After weighting, nivolumab 1 mg/kg + ipilimumab 3 mg/kg was associated with an investigator-assessed ORR of 30.7%, which was nominally higher than that of nivolumab 3 mg/kg monotherapy (19.8%), with a difference in ORR of 10.9% (95% CI: -4.3 to 26.2%; p = 0.161). The BICR-assessed ORR for nivolumab 1 mg/kg + ipilimumab 3 mg/kg (35.9%) was more than twofold higher than that of nivolumab 3 mg/kg monotherapy (14.9%), corresponding to a statistically significant difference in ORR (21.0% [4.5–37.5%]; p = 0.013) after weighting.

The survival outcomes for the nivolumab 1 mg/kg + ipilimumab 3 mg/kg versus nivolumab 3 mg/kg monotherapy before and after weighting are presented in Figure 2. Before weighting, patients treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg had a longer median survival time compared with those treated with monotherapy (22.8 vs 15.2 months; Figure 2A). This difference was even more pronounced after weighting (29.6 vs 14.8 months; Figure 2B). Before weighting, nivolumab 1 mg/kg + ipilimumab 3 mg/kg was nominally associated with a lower risk of all-cause mortality compared with nivolumab monotherapy (HR: 0.66 [95% CI: 0.44–1.01]; p = 0.055; Figure 2A). After weighting, there was a statistically significant reduction in the risk of all-cause mortality among patients treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg versus nivolumab monotherapy (HR: 0.58 [0.35–0.96]; p = 0.034; Figure 2B).

Discussion

The present study assessed the comparative efficacy of nivolumab 1 mg/kg + ipilimumab 3 mg/kg versus other approved second-line treatments for advanced HCC using a combination of MAIC and NMA and a propensity score

weighting analysis. This study found that nivolumab 1 mg/kg + ipilimumab 3 mg/kg as a second-line treatment for advanced HCC had a significantly higher ORR and significantly prolonged OS compared with cabozantinib 60 mg, regorafenib 160 mg and nivolumab 3 mg/kg monotherapy.

In recent years, cancer immunotherapy has seen a rapid expansion of treatment options with promising efficacy results [32]. However, current clinical guidelines from the National Comprehensive Cancer Network for hepatobiliary cancers [33] are largely based on evidence published prior to the approval of more recent immunotherapies for this indication. The present study found that nivolumab 1 mg/kg + ipilimumab 3 mg/kg was associated with statistically higher ORR than existing second-line treatments. Prior evidence suggests that patients with objective responses generally have better survival outcomes [34], which is supported by the improved survival in the nivolumab 1 mg/kg + ipilimumab 3 mg/kg group in the present study. Studies of sorafenib and lenvatinib have shown that postprogression survival can be influenced by clinical factors, such as performance status and Child–Pugh score [35,36], as well as choice of second-line therapy [37]. In the CheckMate 040 study, nivolumab 3 mg/kg every 2 weeks was associated with nonconventional clinical benefit in a subset of patients who achieved a best overall response of progressive disease [38]. Nonconventional benefit was defined as progression followed by stabilization or decrease in target lesion and was associated with OS benefit [38]. These findings provide valuable insights that could inform treatment selection for patients with advanced HCC.

On a mechanistic level, the proposed advantage of combination therapy is a synergistic interaction between two immune checkpoint inhibitors–nivolumab, a PD-1 inhibitor, and ipilimumab, a CTLA-4 inhibitor [39]. Briefly, the CTLA-4 pathway primarily regulates T-cell activation at the early stages in lymph nodes/tissues, while the PD-1 pathway regulates previously activated T-cells at the later stages of an immune response, mainly in peripheral tissues [40,41]. Simultaneous blocking of both pathways may result in enhanced T-cell activity and counteract the compensatory upregulation of additional immune checkpoint inhibitors that is thought to limit the efficacy of monotherapy [42], thereby producing a greater benefit than either therapy alone [39,43]. In contrast to multitargeted kinase inhibitors, immunotherapy targets specific pathways and mutations; therefore, individualized treatment is key to improving clinical outcomes.

One unique aspect of the present study is the hybrid approach, combining MAIC and NMA to conduct indirect treatment comparisons. The use of MAIC established an association of nivolumab 1 mg/kg + ipilimumab 3 mg/kg with placebo while minimizing the cross-trial differences in patient populations. The results enabled the connection between nivolumab 1 mg/kg + ipilimumab 3 mg/kg and other key comparators in the second-line setting in the NMA. Another strength of this study is the use of the propensity score weighting method in comparing nivolumab 1 mg/kg + ipilimumab 3 mg/kg with nivolumab monotherapy, which balanced key patient prognostic factors and controlled potential confounding.

Certain limitations should be considered when interpreting the study results. First, the number of trials included in this study is relatively small, which may affect the precision of the effect estimates. However, this may be mitigated by the similarity of the patient populations across the trials. Second, although pembrolizumab monotherapy has been FDA approved as a second-line treatment for HCC, it could not be included in the NMA because the pivotal trial publications did not report investigator-assessed ORR. Third, we cannot rule out unmeasured or unmatched cross-trial differences (e.g., disease etiology, macrovascular invasion, extrahepatic spread) in the MAIC analysis, which may affect the estimates for comparative efficacy. In addition, traditional limitations of NMA due to variations in first-line therapies, treatment regimens, study populations, outcome definitions and conduct of the trials also apply to this study. Fourth, tolerability was not included in the present analysis although it plays an important role in the selection of agents for second-line treatment of advanced HCC. Finally, the generalizability of the results may be limited, as patients with advanced HCC enrolled in clinical trials may differ from patients with advanced HCC from the general patient population. For example, most patients in the clinical trials had Child–Pugh class A, while in real-world settings, patients could have more impaired liver function with Child–Pugh classes B and C. Evidence from the CheckMate 040 study suggested that nivolumab 240 mg every 2 weeks showed promising efficacy and tolerability in patients with Child–Pugh B status compared with historical data, but further investigation is needed [44]. Consequently, future studies investigating the comparative effectiveness of nivolumab 1 mg/kg + ipilimumab 3 mg/kg versus other approved second-line treatments for advanced HCC in the real-world setting are needed.

Conclusion

Using NMA and MAIC methodology, our study demonstrates a superior efficacy profile of nivolumab 1 mg/kg + ipilimumab 3 mg/kg compared with cabozantinib, regorafenib and nivolumab monotherapy as second-line treatment for advanced HCC.

Summary points

- The combination of nivolumab 1 mg/kg + ipilimumab 3 mg/kg has demonstrated promising efficacy for advanced hepatocellular carcinoma in the second-line setting, but head-to-head trials comparing the efficacy of this combination to other second-line treatments are lacking.
- The objective of this study was to compare efficacy outcomes for nivolumab 1 mg/kg + ipilimumab 3 mg/kg versus cabozantinib 60 mg and regorafenib 160 mg using a matching-adjusted indirect model and network meta-analysis.
- Nivolumab 1 mg/kg + ipilimumab 3 mg/kg was associated with significantly higher objective response rate and prolonged overall survival compared with the other second-line treatments assessed.
- The efficacy profile of nivolumab 1 mg/kg + ipilimumab 3 mg/kg was superior to that of the other second-line treatments for advanced hepatocellular carcinoma.

Author contributions

All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Financial & competing interests disclosure

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Ethical conduct of research

The present investigation was based on previously conducted studies and does not contain any procedures with human participants or animals performed by any of the authors.

Data sharing statement

The analysis contained a meta-analysis that used published data from clinical trials. The matching-adjusted indirect comparison and propensity score weighting analyses used individual patient data from the CheckMate 040 study provided by Bristol Myers Squibb.

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