Hepatobiliary & Pancreatic Diseases International 18 (2019) 505–510

Contents lists available at ScienceDirect

Hepatobiliary & Pancreatic Diseases International

journal homepage: www.elsevier.com/locate/hbpd

Meta-analysis

PD-1 inhibitors monotherapy in hepatocellular carcinoma: Meta-analysis and systematic review

Ioannis A. Voutsadakis [a,b,*]

[a] Algoma District Cancer Program, Sault Area Hospital, Sault Ste. Marie, Ontario, Canada
[b] Section of Internal Medicine, Division of Clinical Sciences, Northern Ontario School of Medicine, Sudbury, Ontario, Canada

ARTICLE INFO

Article history:
Received 19 June 2019
Accepted 11 September 2019
Available online 14 September 2019

Keywords:
Hepatocellular carcinoma
Immune checkpoint inhibitors
Nivolumab
Pembrolizumab
Meta-analysis

ABSTRACT

Background: Immunity plays a major role in carcinogenesis and this is the case also for hepatocellular carcinomas (HCC). Checkpoint inhibitors, novel drugs that enhance the immune system's ability to attack cancers, have been successfully introduced for the therapy of various malignancies including HCC. An important target of these drugs is the PD-L1/PD-1 ligand/receptor pair and several clinically available inhibitors of this pair exist.

Data sources: A search of the literature until April 20, 2019 was performed in the MEDLINE/PubMed database, the Embase database and the Cochrane Central Register of Controlled Trials. The clinical studies describing treatment with PD-L1/PD-1 inhibitors as monotherapy in HCC patients were retrieved. Patient characteristics with relevance for treatment efficacy, such as liver function, disease extend and previous treatment, were extracted from identified articles. Response and survival outcomes were the primary focus of the meta-analysis. Summary estimates of response rates and survival were calculated using a random or fixed effect model, depending on heterogeneity. Most common adverse effects were also recorded and summarized.

Results: Three studies (two on nivolumab and one on pembrolizumab) with a total of 400 patients were included in the analysis. The summary response rate (RR) was 17.3% [95% confidence interval (CI): 13.2%–21.4%]. The summary disease control rate (DCR) was 56.6% (95% CI: 44.7%–68.5%). Summary progression free survival (PFS) was 3.5 months (95% CI: 2.8–4.2 months). Summary overall survival (OS) was 10.4 months (95% CI: 3.5–17.2 months). Adverse effect rate was low and also consistent with the adverse effect profile of PD-L1/PD-1 inhibitors in other disease locations.

Conclusions: Pembrolizumab and nivolumab are the only checkpoint inhibitors with data in HCC. Meta-analysis of their effectiveness discloses rates not dissimilar to other systemic therapies available for this disease. Of interest also are the observed long responses in a sub-set of responders. Further development is clearly warranted.

Introduction

Hepatocellular carcinoma (HCC) constitutes a major public health problem especially in areas of the world where viral hepatitis is more prevalent. Even in western countries liver cancers are in the top ten list of cancer mortality [1]. Despite improved anti-viral treatments that are expected to reduce the burden of HCC in the future, the disease is forecasted to remain a significant burden for the coming decades. In addition, prevalence of HCC related to other reasons such as non-viral steatohepatitis and alcohol-related cases remains high [2]. Liver cancer is the fifth most prevalent cancer in men worldwide, after lung, prostate, colorectal and gastric cancer, with an estimated number of 554,000 new cases and an estimated 521,000 deaths [3]. In women it is the ninth most prevalent cancer with 228,100 cases worldwide and 224,500 deaths. A significant proportion of this burden is observed in developing countries [3].

Immune blockade inhibitors (also called immune checkpoint inhibitors; ICIs) represent a novel class of monoclonal antibody drugs that bind and inhibit the function of inhibitory immune receptors and release the immune anti-neoplastic response [4]. ICIs that are currently available for clinical use include CTLA-4 (cytotoxic T lymphocyte antigen 4), PD-1 (programmed death 1) and its ligand PD-L1. Other immune inhibitory receptor blockers, such as the macrophage inhibitor Hu5F9-G4 blocking the

* Correspondence to: Algoma District Cancer Program, Sault Area Hospital, 750 Great Northern Road, Sault Ste Marie, ON P6B 0A8, Canada.
E-mail address: ivoutsadakis@nosm.ca

https://doi.org/10.1016/j.hbpd.2019.09.007
1499-3872/

eat-me-not receptor CD47, are in developing process and will probably be available for clinical use in the near future [5]. Currently approved monoclonal antibodies blocking CTLA-4 include ipilimumab and tremelimumab. PD-1 receptor blockers include nivolumab, pembrolizumab and cemiplimab. Drugs inhibiting PD-L1 include atezolizumab, avelumab and durvalumab. One or more ICIs have been approved for use in various malignancies, such as lung cancer, melanoma, urothelial and renal carcinomas, Hodgkin's lymphoma, squamous carcinomas of the skin as well as HCC and other gastrointestinal cancers [6–15]. One of the ICIs, pembrolizumab has also a site agnostic indication for any tumor with microsatellite instability (MSI), being the first cancer drug with approval not based on site [16]. ICIs have been effective in malignancies refractory to chemotherapy such as metastatic melanoma and renal carcinomas and have outperformed chemotherapy in sub-sets of other cancers such as lung carcinomas and urothelial carcinomas, at least in second line [6,8,17]. ICIs have been studied in clinical trials for many common gastrointestinal cancers [18].

HCC, when beyond the indications for local treatments such as surgical resection and ablative techniques, has few systemic treatment options. Thus new options have been sought. Herein, a systematic review and meta-analysis of studies of PD-1 or PD-L1 inhibitors as monotherapy in HCC is presented.

Methods

A search of the literature was performed in the MEDLINE/PubMed database (www.ncbi.nlm.nih.gov/pubmed), the EMBASE (Excerpta Medica) database and the Cochrane Central Register of Controlled Trials. Search terms used were "nivolumab" OR "pembrolizumab" OR "atezolizumab" OR "avelumab" OR "durvalumab" OR "cemiplimab" AND "hepatocellular carcinoma" OR "hepatoma". Date of last search of the databases was April 20, 2019. The searched for medications, PD-1 inhibitors nivolumab, pembrolizumab and cemiplimab and PD-L1 inhibitors atezolizumab, avelumab and durvalumab have been approved for clinical use in various cancers. Phase II and III studies and case series that included monotherapy arms of any of these inhibitors in locally advanced and metastatic HCC were eligible for inclusion in the meta-analysis. Other inclusion criteria were articles in English language and presentation of data for any of the efficacy outcomes of interest that were response rate (RR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). Papers in other languages than English, case reports, small non-randomized case studies with less than 5 patients, pre-clinical studies or reviews and opinion articles and studies published only in abstract form were excluded. Studies of combination therapies of PD-1/PD-L1 inhibitors with other checkpoint inhibitors, other targeted drugs or chemotherapeutics were also excluded. A manual search of references of retrieved articles was undertaken for identification of additional studies of interest.

Included trials and series were reviewed in detail for extraction of data on the demographics of patient populations, extend of the disease and the efficacy and toxicity of treatment. Demographic data of interest extracted for the analysis included age of the patients, Eastern Cooperative Oncology Group performance status (ECOG PS), number and type of previous treatments for advanced disease and whether the patient had prior hepatectomy or other local treatments. Additional data of interest included positivity for PD-L1, presence of MSI and tumor mutation. These biomarkers have been associated with PD-L1/PD-1 immunotherapy responses in previous investigations. Efficacy outcomes of interest included were RR, DCR, median PFS and median OS. The 95% confidence intervals (CI) of all efficacy outcomes were recorded or calculated from the data in the articles. All grade and grade 3 and 4 toxicity data were also captured from included studies and presented in a cumulative table. Risk of bias in the included studies was evaluated with the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) assessment tool [19].

Descriptive statistics such as percentages were calculated for the pooled analysis of each characteristic of interest across included studies. Outcome rates were weighted according to the number of patients in each series. Heterogeneity among the studies was estimated with the Cochran's Q and I^2 tests. An I^2 of $>50\%$ is considered as denoting high heterogeneity and a random effect model is employed. High I^2 is associated with a high Q statistic that produces statistically significant P values ($P<0.05$). In cases of I^2 between 15% and 50% moderate heterogeneity exists and still a random effect model is preferable [20]. Calculations were performed in Excel (Microsoft Corp., Redmond, WA) as previously described with some modifications [21,22] and confirmed with the open-source online software Open Meta-analyst, developed at Brown University, Providence, RI, U.S.A. and freely available (www.cebm.brown.edu/openmeta/) [23]. The two tools produced similar results and only the first analysis is presented in the figures.

Results

The initial search produced 96 articles. The search for nivolumab in HCC returned 56 articles, the search for pembrolizumab returned 26 publications, 7 publications were discovered on durvalumab, 4 on atezolizumab, 2 on avelumab and 1 on cemiplimab (Fig. 1). Ninety-three articles did not meet the inclusion criteria for different reasons detailed in Fig. 1 and were excluded. The most common reasons of exclusion were that the paper concerned a review or opinion piece, a case report or it studied a different medication than the medication searched for (Fig. 1). Three studies [24–26] were retained for the meta-analysis with a total of 400 patients. Two of them [24,26] concerned nivolumab and one [25] was on pembrolizumab, while no articles were found on any of the other four inhibitors (Table 1). The articles included in the meta-analysis were published in 2017, 2018 and 2019, respectively. Two articles, one [24] concerning nivolumab and another [25], pembrolizumab, were prospective studies. The study of pembruliizumab [25] was a phase 2 trial, while the nivolumab study [24] was a phase 1/2 trial with an escalation phase that included 48 patients, most receiving a dose of 3 mg/kg every 2 weeks or more, and an expansion phase that included 214 patients

Table 1
The three studies included in the current meta-analysis.

Studies	Study registration no.	Year of publication	Country	Total number of patients	Inhibitor	Line of treatment	RR (%)	DCR (%)
El-Khoueiry et al. [24]	NCT01658878	2017	Global	262	Nivolumab	Mostly post-sorafenib	14.6 (escalation) 19.6 (expansion)	58.33 (escalation) 64.48 (expansion)
Zhu et al. [25]	NCT0270414	2018	Global	104	Pembrolizumab	Post-sorafenib	17.3	61.53
Finkelmeier et al. [26]	–	2019	Germany	34	Nivolumab	Mostly post-sorafenib	11.8	35.29

RR: response rate; DCR: disease control rate.

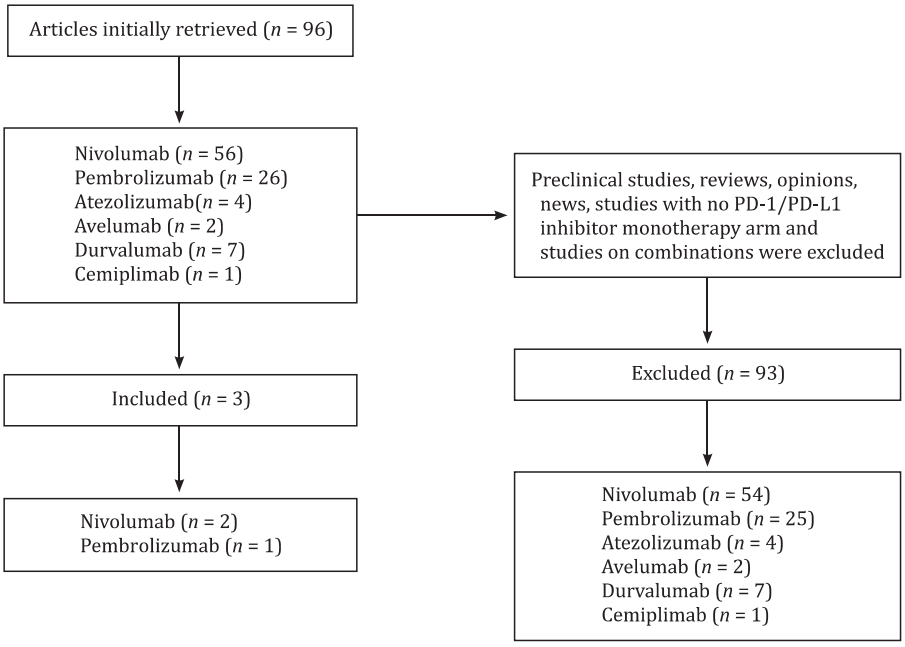

Fig. 1. Flow diagram of the studies evaluated for the meta-analysis and reasons for exclusion.

treated at the level of 3 mg/kg (Table 1). The pembrolizumab study used a fixed dose at 200 mg every 3 weeks [25]. Finkelmeier et al. study [26] was retrospective and centered on nivolumab. Zhu et al. study [25] included exclusively patients in the second line of systemic treatment after sorafenib, while the two other reports [24,26] included patients in the first and second line treatment, although most patients in these studies had previously received sorafenib.

The median age of the patients in the included studies were as follows: escalation cohort 62 years (range 55–69) [24], expansion cohort 64 years (range 56–70) [24], 68 years (IQR 62–73) [25], 65 years (range 40–77) [26]. Patients in the three included studies had a median age between 62 and 68 years with a range from 40 to 77 years. About 79.8% patients were men and most patients (59%) had an ECOG PS of 0 and the rest had predominantly an ECOG PS of 1 (Table 2). Regarding the Child–Pugh classification, 93.8% of patients were Child–Pough A. A total of 186 patients (46.5%) in the three studies were infected with hepatitis B or hepatitis C virus. Extrahepatic extension of the cancer and vascular invasion were present in 66.0% and 29.8% of patients, respectively. Most patients (82.7%) had received prior systemic therapy (sorafenib), while the rest (17.3%) were treated in the first line setting. Among the patients for whom this information was reported, 52.7% and 58.4% had previous local treatments or surgical treatments, respectively (Table 2). The PD-L1 status was known in 270 patients and was positive in only 67 of them (24.8%). MSI or the tumor mutation burden was not reported in any of the studies.

Risk of bias is estimated to be moderate in all three studies due to their phase II non-randomized design or retrospective design [24–26]. These biases could be in the domain of intervention assignment due to selection of patients for inclusion and in the domain of outcomes measurement, especially in the retrospective study, where ascertaining of responses to therapy may be problematic. In all three studies, authors included patients with similar baseline ECOG PS (S = status) (mostly 0) and Child-Pugh category (mostly A) in order to minimize confounding but other factors such as extend of disease and previous local treatments may still have influenced outcomes.

Table 2
Characteristics of the included patients from the studies of immune checkpoint inhibitors in HCC (n = 400).

Characteristics	Data (n,%)
Sex	
Male	319 (79.8%)
Female	81 (20.2%)
ECOG PS	
0	236 (59.0%)
1	161 (40.3%)
2	3 (0.7%)
Child-Pough score	
A	375 (93.8%)
B	24 (6.0%)
C	1 (0.2%)
Viral hepatitis	
Negative	214 (53.5%)
HCV	96 (24.0%)
HBV	90 (22.5%)
Vascular invasion	
Positive	119 (29.7%)
Negative	281 (70.3%)
Extrahepatic disease	
No	136 (34.0%)
Yes	264 (66.0%)
Prior lines of therapy	
0	69 (17.3%)
1	331 (82.7%)
Prior local treatment[a]	
No	140 (47.3%)
Yes	156 (52.7%)
Prior surgery[a]	
No	123 (41.6%)
Yes	173 (58.4%)
PD-L1[b]	
Positive	67 (18.3%)
Negative	203 (55.5%)
Unknown	96 (26.2%)

Some characteristics were available in only part of the studies.
[a] two studies (n = 296) [24,26].
[b] two studies (n = 366) [24,25]. Intestinal histologic type includes variants.

Studies	RR%	95% CI
El-Khoueiry et al expanded	19.6	13.7 - 25.5
El-Khoureiry et al escalation	14.6	3.8 - 25.4
Zhu et al	17.3	9.3 - 25.3
Finkelmeier et al	11.8	0.3 - 23.3
Summary	17.3	13.2 - 21.4

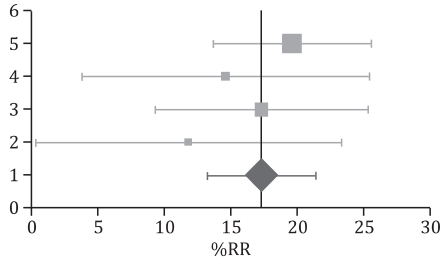

Fig. 2. Diagram of response rates (RR) and 95% confidence intervals (CI) of studies of PD-1 inhibitors in hepatocellular carcinoma.

Studies	DCR%	95% CI
El-Khoueiry et al expanded	64.5	53.7 - 75.2
El-Khoureiry et al escalation	58.3	36.7 - 79.9
Zhu et al	61.5	46.5 - 76.6
Finkelmeier et al	35.3	15.3 - 55.3
Summary	56.6	44.7 - 68.5

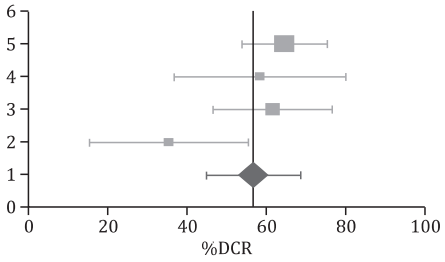

Fig. 3. Diagram of meta-analysis of disease control rates (DCR) and 95% confidence intervals (CI).

Studies	PFS months	95% CI
El-Khoueiry et al expanded	4.0	2.9 - 5.4
El-Khoureiry et al escalation	3.4	1.6 - 6.9
Zhu et al	3.2	2.2 - 4.1
Summary	3.5	2.8 - 4.2

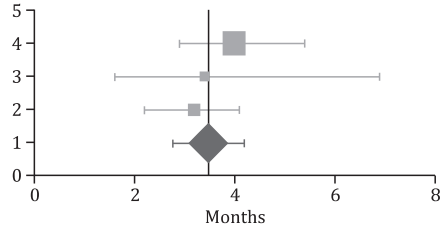

Fig. 4. Diagram of progression-free survival (PFS). One of the three studies that are included in the report did not provide information on PFS and thus the PFS analysis and summary estimates of PFS are based on the remaining two studies.

Studies	OS months	95% CI
El-Khoueiry et al expanded	15.0	9.6 - 20.2
Zhu et al	12.9	9.7 - 15.5
Finkelmeier et al	3.6	0 - 7.1
Summary	10.4	3.5 - 17.2

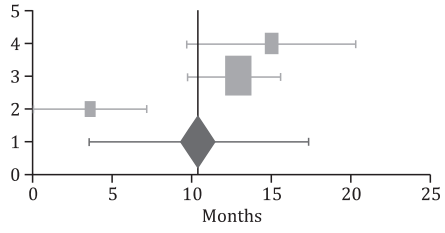

Fig. 5. Meta-analysis of overall survival (OS) and 95% confidence intervals (95% CI).

The nivolumab phase 1/2 study provided all efficacy outcomes in the escalation and expansion phase separately and thus the meta-analysis treated them separately, except for the OS analysis where only data from the escalation phase were included, as the OS of the expansion phase was not reached at the time of the article publication. The meta-analysis for RR based on all 400 patients disclosed a summary RR of 17.3% (95% CI: 13.2%–21.4%) (Fig. 2). RR analysis was performed using the fixed effect model, as evaluation for heterogeneity between studies confirmed a low level of heterogeneity with an I^2 value of 0 (Cochran's $Q=1.71$, χ^2 $P=0.35$).

DCR was also based on all 400 patients. Summary DCR was 56.6% (95% CI: 44.7%–68.5%) (Fig. 3). The three studies had intermediate heterogeneity in their DCR estimations with an I^2 value of 54.01% (Cochran's $Q=6.52$, χ^2 $P=0.12$). Thus, the random effect model was used in the analysis.

Finkelemeier et al. study [26] did not provide data of PFS and thus the PFS meta-analysis included only the two other studies [24,25] with a total of 366 patients. The level of heterogeneity was low ($I^2=0$, Cochran's $Q=1$, χ^2 $P=0.6$) and the analysis was performed under the fixed effect model. Summary PFS was 3.5 months (95% CI 2.8–4.2 months) (Fig. 4).

As mentioned, OS of the expansion phase of the phase 1/2 study was not reached and the analysis for OS included patients from the escalation phase of this study [24] and the two other studies [25,26]. The total number of patients in the OS analysis was 186. The meta-analysis disclosed a summary OS of 10.4months (95% CI: 3.5–17.2 months) (Fig. 5). This analysis was performed under the random effect model as the level of heterogeneity between studies was high ($I^2=89\%$, Cochran's $Q=19.74$, χ^2 $P=0.0004$).

RR was reported separately for patients that were positive and negative for PD-L1 in 270 patients from two studies [24,25]. Among the 67 patients who were PD-L1 positive, 19 patients (28.4%) showed response to the ICIs, while 36 of 203 patients (17.7%) who were PD-L1 negative had response.

Regarding adverse effects, treatment with nivolumab and pembrolizumab was well tolerated and no unusual adverse effects besides the well-known adverse effect profile of the drugs was reported (Table 3). Common all grades adverse effects observed in

Table 3
All grade and grade 3–4 toxicities observed in the two most extensive included studies.

Toxicity	All grades/total number toxicity information mentioned	Grade 3–4/total number toxicity information available
Asthenia/fatigue	81/366 (22.1%)	8/366 (2.2%)
Neutropenia	0	0
Febrile neutropenia	0	0
Anemia	7/366 (1.9%)	2/366 (0.5%)
Lung infection/ pneumonia	1/366 (0.3%)	1/ 366 (0.3%)
Nausea	28/366 (7.7%)	0
Diarrhea	43/366 (11.7%)	3/366 (0.8%)
Inappetance	23/366 (6.3%)	2/366 (0.5%)
Pruritus/cutaneous rash	125/366 (34.2%)	3/366 (0.8%)
Immune related		
Hyperthyroidism	1/104 (1.0%)	0
Hypothyroidism	6/104 (5.8%)	0
Colitis	1/104 (1.0%)	0
Adrenal insufficiency	2/104 (1.9%)	2/104 (1.9%)
Hepatitis enzymes elevation	50/366 (13.7%)	33/366 (9.0%)

Some toxicities were included in the toxicity discussion of one study but not the other and thus the denominator is less than the total of 366 patients included in the two studies.

more than 10% of patients were asthenia and pruritus or cutaneous rashes but corresponding grade 3 or 4 asthenia or rashes were rare (Table 3). Severe immune related adverse effects were also rare, except for grade 3 and 4 hepatic enzymes elevations that were observed in 9% of patients. The underlying cancer may have contributed to this adverse effect, although similar elevations have been observed with the use of these medications on other types of cancer.

Discussion

HCC remains a disease with poor prognosis especially in advanced stages [3]. Systemic treatments are the main option of treatment in advanced stage of HCC. Despite expanded options that include now sorafenib and lenvatinib in the first line and regorafenib, cabozantinib and ramucirumab in the second line, estimated survival remains at or below one year. Thus, new therapies are still needed. Immunotherapy with PD-L1 and PD-1 inhibitors has been successful in extending survival in several other cancers. In some cases, such as metastatic melanoma, impressive results have been obtained in a sub-set of patients [9]. Thus, ICIs have been studied in several additional cancer types, among which is HCC, to establish if they could constitute an effective option of treatment. These drugs are monoclonal antibodies that activate the immune system to mount an anti-tumor response by blocking the interaction of the inhibitory PD-L1/PD-1 ligand/receptor pair. Both effector cytotoxic T cells and NK cells express PD-1 and may become activated after blockade of the receptor or its ligand to attack tumor cells if appropriate neo-antigens are presented in the tumor cells' surface [27]. The best responses with PD-L1 and PD-1 inhibitors have been obtained in tumor types with high mutation burdens such as lung cancers and melanoma as well as tumors with microsatellite instability independently of primary site [6,9,16].

The current systematic review and meta-analysis focused on PD-L1 and PD-1 inhibitors in HCC. The analysis of the three studies estimated a RR of about 17.3% and a DCR of 56.6% for the PD-1 inhibitors nivolumab and pembrolizumab in patients with HCC. Summary PFS was 3.5 months and summary OS was 10.4 months. These results, although overall mediocre, have to be evaluated against other systemic treatments available for this disease. In a randomized phase 3 trial of sorafenib versus placebo as a first line systemic treatment in a similar population of hepatocellular carcinoma patients predominantly with Child-Pugh class A cirrhosis and ECOG PS of 0 or 1, sorafenib treatment has resulted in a median OS of 10.7 months (95% CI: 9.4–13.3 months) [28]. In a similar randomized trial from Asia in patients with a heavier tumor burden, the sorafenib arm had a median OS of 6.5 months (95% CI: 5.5–7.5 months) [29]. In another randomized phase 3 trial comparing sorafenib to another multi-kinase inhibitor, lenvatinib, in the first line setting, median OS in the sorafenib arm was 12.3 months (95% CI: 10.4–13.9 months) and in the lenvatinib arm it was 13.6 months (95% CI: 12.1–14.9 months) [30]. Although a direct comparison of these treatments with ICIs will provide more robust data and a trial comparing sorafenib with nivolumab is ongoing, available data as summarized in the current meta-analysis suggest that efficacy of these immunotherapeutics are in the range of other available first line treatments. Moreover, ICIs are well-tolerated and produce some long-term responses in responding patients [25]. The challenge in HCC, similarly to other cancers, will identify optimal biomarkers to predict patients that will respond and obtain a benefit from the drugs. Biomarkers will also provide the opportunity for a prior identification of non-responders that could be treated with alternative drugs or could be candidates for treatment with combinations of ICIs with other immune modifiers that may boost immune response. The three main biomarkers of response to ICIs studied in other cancer types include expression of PD-L1 by immunohistochemistry, MSI status and tumor mutation burden. Among them, PD-L1 expression was the only one that was included in the analysis of some of the patients in the studies in HCC [24,25]. This evaluation suggests that patients that express the ligand may have a higher probability of response. However, responses have also been seen among patients that were negative for PD-L1.

The evaluation of adverse effects of PD-1 inhibitors in the studies of HCC included in this systematic review was reassuring in that it did not disclose any new specific adverse effects related specifically to the disease. Immune related adverse effects were overall rare, including liver-specific immune effects.

Limitations of the present meta-analysis consist mostly of the aforementioned lack of information regarding predictive markers that could enrich for responding patients and guide further development. Another limitation is that only anti-PD-1 drugs (nivolumab and pembrolizumab) published as a full paper were included. Despite clinical similarities produced from inhibition of the same pair of immune ligand/receptor, the expression of PD-1 and PD-L1 proteins varies in the tumor cells, immune cells and other cells that are components of the tumor micro-environment and this may theoretically lead to disparate therapeutic outcomes. However, although no direct comparisons are available for any

disease, in clinical practice observed outcomes seem to be similar. Finally, the inclusion of patients from the escalation phase of one of the included studies may have decreased the observed efficacy in the meta-analysis, but differences in the RR between the escalation and expansion cohort have been small (14.6% vs 19.6%) [24].

The study of the ICIs in HCC is still in its early phase and this is depicted in the current systematic review and meta-analysis. Additional studies that include arms with these drugs are under way and will enrich the field of knowledge.

Despite low response rates and limited overall survival benefits with ICIs in HCC, further studies are warranted and better tailored treatment as well combinations may be avenues to explore for further building on the potential of this promising class of antineoplastic agents.

Contributors

VIA conceived the study, performed the research and wrote the manuscript. VIA is the guarantor.

Funding

None.

Ethical approval

Not needed.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
[2] Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723–750.
[3] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[4] Voutsadakis IA. Immune blockade inhibition in breast cancer. Anticancer Res 2016;36:5607–5622.
[5] Advani R, Flinn I, Popplewell L, Forero A, Bartlett NL, Ghosh N, et al. CD47 blockade by Hu5F9-G4 and rituximab in non-Hodgkin's lymphoma. N Engl J Med 2018;379:1711–1721.
[6] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627–1639.
[7] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018–2028.
[8] Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373:123–135.
[9] Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320–330.
[10] Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014;515:558–562.
[11] Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803–1813.
[12] Chen R, Zinzani PL, Fanale MA, Armand P, Johnson NA, Brice P, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol 2017;35:2125–2132.
[13] Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med 2018;379:341–351.
[14] Kudo T, Hamamoto Y, Kato K, Ura T, Kojima T, Tsushima T, et al. Nivolumab treatment for oesophageal squamous-cell carcinoma: an open-label, multicentre, phase 2 trial. Lancet Oncol 2017;18:631–639.
[15] Shitara K, Özgüroğlu M, Bang YJ, Di Bartolomeo M, Mandalà M, Ryu MH, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet 2018;392:123–133.
[16] Lemery S, Keegan P, Pazdur R. First fdaFDA approval agnostic of cancer site—when a biomarker defines the indication. N Engl J Med 2017;377:1409–1412.
[17] Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015–1026.
[18] Stein A, Moehler M, Trojan J, Goekkurt E, Vogel A. Immuno-oncology in giGI tumours: clinical evidence and emerging trials of PD-1/PD-L1 antagonists. Crit Rev Oncol Hematol 2018;130:13–26.
[19] Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
[20] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560.
[21] Neyeloff JL, Fuchs SC, Moreira LB. Meta-analyses and forest plots using a microsoft excel spreadsheet: step-by-step guide focusing on descriptive data analysis. BMC Res Notes 2012;5:52.
[22] Voutsadakis IA. A systematic review and pooled analysis of retrospective series of eribulin in metastatic breast cancer. Anticancer Drugs 2017;28:557–564.
[23] Wallace BC, Schmid CH, Lau J, Trikalinos TA. Meta-Analyst: software for meta–analysis of binary, continuous and diagnostic data. BMC Med Res Methodol 2009;9:80.
[24] El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, 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 2017;389:2492–2502.
[25] Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol 2018;19:940–952.
[26] Finkelmeier F, Czauderna C, Perkhofer L, Ettrich TJ, Trojan J, Weinmann A, et al. Feasibility and safety of nivolumab in advanced hepatocellular carcinoma: real-life experience from three German centers. J Cancer Res Clin Oncol 2019;145:253–259.
[27] Voutsadakis IA. Immune ligands for cytotoxic T Lymphocytes (CTLS) in Cancer Stem Cells (CSCS). Front Biosci (Landmark Ed) 2018;23:563–583.
[28] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.
[29] Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25–34.
[30] Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163–1173.