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Review Article

Toxicity of Immune Checkpoint Combination Therapy in Advanced Renal Cell Carcinoma: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Abstract

Background: Novel combination strategies have improved outcomes in metastatic renal cell carcinoma (mRCC). However, the incidence and risk of overlapping adverse events (AE) with double ICI or ICI-TKI combinations remains unknown. The aim of this study is to investigate the risk of such potentially simultaneous AEs with combination strategies compared to sunitinib alone in mRCC patients through a meta-analysis of randomized clinical trials (RCT).

Methods: PubMed was reviewed for phase III RCT trials with ICI combination therapies in mRCC. The odd ratios (OR) of any-grade and high-grade (g3-5) hepatotoxicity (AST and ALT elevations), hypothyroidism, diarrhea, cutaneous toxicity (rash), hypertension and creatinine elevation were pooled for meta-analysis. Fixed or random- effects models were used to calculate ORs depending on the grade of heterogeneity.

Results: Five phase III RCT, accounting for 4726 patients, were eligible and included in the analysis. All studies compared double ICI or ICI-TKI combinations with sunitinib. ICI combination was associated with a significantly increased OR of any-grade (AST, OR: 1.52, p = 0.01; ALT, OR:1.79, p=0.01) and high-grade (AST, OR: 2.78, p <0.001; ALT, OR: 3.15, p<0.001) hepatotoxicity, and any-grade (OR: 1.85, p<0.001) and high-grade (OR:4.56, p<0.001) rash. Any-grade hypothyroidism and both any-grade and high-grade diarrhea and hypertension (p<0.001) were more common with IC-TKI compared with double ICI

Conclusion: The use of ICI combination therapy increases the risk of hepatotoxicity and rash, compared to sunitinib monotherapy regardless the type of combination therapy (double ICI or ICI-TKI). The risk of hypothyroidism, diarrhea as well as hypertension is lower with the double ICI combination compared to ICI-TKI. This meta-analysis may add some insights in treatment selection based on patient profile and potential risk of toxicities.

Keywords: immune checkpoint inhibitors, immune-related adverse events, hepatotoxicity, renal cell carcinoma, tyrosine kinase inhibitors

Introduction

Renal Cell Carcinoma (RCC) is the tenth most common cancer in men and the 16th in women worldwide, accounting for 431.000 cases in 2020 [1]. Although most patients will have localized disease at diagnosis, almost one-third will relapse after surgery and develop distant metastases during the follow-up [2]. The natural history of advanced RCC (mRCC) has dramatically improved during the last decade with the introduction of vascular endothelial growth factor receptor Tyrosine Kinase Inhibitors (TKI) and immune checkpoint inhibitors (ICI) to the treatment landscape [3].

Moreover, during the last years, the management of mRCC has been switched again by the incorporation of ICI combination therapy to the first line setting [4–8]. Firstly, the CHECKMATE 214 demonstrated that the combination of two ICIs, nivolumab-ipilimumab (anti-PD1 and anti-CTLA4), was superior to sunitinib alone in intermediate and poor-IMDC risk patients [4]. However, it failed to demonstrate a survival advantage in favorable-risk patients [4]. Studies have shown that angiogenesis seems to be associated with an immunosuppressive microenvironment, while tumor evasion seems to be linked to angiogenesis [9]. Based on this rationale, several phase III clinical trials have evaluated ICI combination therapies with TKIs compared to sunitinib, demonstrating a significant survival advantage in mRCC patients in all IMDC-risk groups [5–8].

These new ICI combination therapies have shown improved efficacy outcomes but they are also associated with an increased risk of toxicity, which should not be overlooked [4–8]. Both drugs can correlate with a wide range of adverse effects (AE) with particular or shared mechanisms. As an example, among possible adverse effects, hepatotoxicity can be induced by both of them. Tyrosine kinase inhibitors can not only induce hepatotoxicity through mechanisms like the formation of reactive metabolites via the cytochrome p450, impaired hepatic bile acid transport, or mitochondrial dysfunction, but can also cause pathological immune responses that could enhance ICI-mediated immunotoxicity [10]. Regarding the latter, adaptative immunity mechanisms with activation of cytotoxic and autoreactive T-cells, B-cell activation, and antibody formation as well as cytokine expression have been proposed as some of the mechanisms explaining ICI-related toxicity in common organ sites, including cutaneous, endocrinopathies, nephritis, gastrointestinal alterations such as diarrhea/colitis, among others [11,12]. Given the shared adverse effects profile of both drug families, a combination therapy strategy would be expected to increase the risk of developing this type of adverse events.

Hepatotoxicity, defined as elevations in aspartate aminotransferase (AST) or alanine aminotransferase (ALT), hypothyroidism, diarrhea, cutaneous toxicity (rash), hypertension, and creatinine increase were certain and relevant monitored and reported AEs through all the pivotal trials evaluating front-line ICI combination therapy [4–8]. Given the recent approvals of several ICI combination therapies as first-line treatment in mRCC, we conducted a meta-analysis to determine the risk of developing these adverse events with combination therapy (double ICI and ICI-TKI) compared to sunitinib alone.

Methods

This analysis has been conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement [13]. We followed the measures described in the Cochrane Handbook for Systematic Reviews of Interventions to pool the evidence [14]. The results of this study are reported following PRISMA guidelines.

Eligibility Criteria

Type of Study Design Included. Randomized Clinical Trials (RCTs) were eligible for inclusion. No language, publication date, or publication status restrictions were imposed.

Type of Participants. The study population consisted of treatment-naive metastatic clear cell RCC patients.

Type of Interventions Included. The experimental arm consisted of ICI combination therapies, including double ICI combination therapy (nivolumab-ipilimumab) and ICI combination therapies with TKI (pembrolizumab-axitinib, pembrolizumab-lenvatinib, avelumab-axitinib or nivolumab-cabozantinib) administered as first-line therapy. Sunitinib alone was used as the control arm in all five trials.

Types of Outcome Measures Included. The primary outcomes were to compare: the incidences and odd ratios of developing any-grade and high-grade (grade ≥3) alterations in commonly encountered clinical parameters (AST and ALT elevations, hypothyroidism, diarrhea, rash, hypertension, and creatinine increase) according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4, between (1) ICI combination therapies and sunitinib alone, (2) double ICI and ICI-TKI combinations, and (3) according to ICI agent.

Information Sources

We searched PubMed, Medline, Embase, and the Cochrane Central Register of Controlled Trials for related studies published before May 5, 2021. Searches were limited to studies published from 2018 onwards. Additionally, https://clinicaltrials.gov, abstracts, and virtual meeting presentations containing the same terms from the American Society of Clinical Oncology (ASCO)

and the European Society of Medical Oncology (ESMO) conference held between January 2018 and June 2020 were also used to identify relevant and ongoing clinical trials.

Search Strategy

The search was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions[14]. Keywords included in the search for eligible trials in the databases mentioned previously: ("immunotherapy" OR "nivolumab" OR "pembrolizumab" OR "atezolizumab" OR "avelumab" OR "ipilimumab" OR "bevacizumab" OR "tyrosine-kinase inhibitor") AND "sunitinib" AND ("renal cell carcinoma" OR "kidney cancer") as a search algorithm. The search was performed using the filter "clinical trials."

Data Collection and Analysis

Study Selection. Two reviewers (LCA, ST) screened all published articles and abstracts of all literature, searched independently, and identified whether the trials met the inclusion criteria as designed and described in this protocol. Disagreement was resolved by discussion and, when needed, by consulting a third author (GDV).

Data Extraction and Management. All citations found during the searches were stored in a reference database. Two authors (LCA, ST) independently performed data extraction. The following data were recorded: author, demographic data, treatment regimens, sample size, and summary estimates of interest outcomes. The outcomes of interest were the incidence of any-grade and high-grade AST/ALT, hypothyroidism, diarrhea, rash, hypertension, and creatinine increase. All this data was recorded in a predesigned table.

Assessment of Risk of Bias (RoB) in Included Studies

Two authors (LCA, ST) assessed the methodological quality of the eligible trials using Cochrane's Risk of Bias (RoB) tool on a three-point scale: high, low, and unclear bias. The quality of evidence was rated according to GRADE methods as high, moderate, low, or very low, based on the risk of bias, directness, precision, and consistency in treatment effects. A high-quality evidence level was assigned to well-designed RCTs with consistent findings (I2 <50%). The quality of evidence was downgraded to moderate if at least one of four criteria was not met, and it was downgraded to low if two or more criteria were not met. We concluded a high risk of bias in the body of evidence if at least one RCT had a high risk of bias. The body of evidence was downgraded when we suspected a high risk of publication bias due to the unavailability of the results in ClinicalTrials.gov or journal articles.

Data Analysis

The heterogeneity between the studies was assessed using Cochran's Q test (in which a P-value<0.05 indicated heterogeneity between studies) and the I-squared statistic (values <25%, 25% to 75%, and >75% were interpreted as low, moderate and high levels of heterogeneity respectively). As there was moderate heterogeneity between trials for some outcomes, random-effects models applying the restricted maximum likelihood (REML) method were used in the meta-analysis. Forest plots were constructed for each outcome, and the pooled effect was calculated using odds ratios (OR) for categorical data, along with their 95% confidence intervals.

Publication Bias

Publication bias was assessed by visual inspection of funnel plots and quantified using Egger's linear regression test. Statistical analysis was performed using Stata software Version 16.

Results

Characteristics of Trials, Patients and Interventions

Our search strategy yielded 360 potentially relevant records on the ICI combination therapy versus sunitinib in mRCC. After matching records from different sources, we obtained five studies investigating the efficacy and safety of ICI combination therapy compared to sunitinib in mRCC (Figure 1).

After 53 duplicates were removed, we screened 307 records. Two hundred eighty-one records were excluded for at least one of the following reasons: letters, case reports, corrections, guidelines, retrospective studies, description only at clinicaltrials.gov, or not related to RCC. Two were excluded for either being phase II trials or subanalyses or versions of included trials. After reviewing the remaining publications, five studies met the criteria for final inclusion in the meta-analysis (Table 1). A total of 4726 patients were available for the meta-analysis. All trials evaluated ICI-TKI combination compared to sunitinib, except for the CHECKMATE 214 assessing double ICI combination (nivolumab-ipilimumab). All of these studies had safety as a secondary endpoint. The evaluation of the AST and ALT elevation, hypothyroidism, diarrhea, rash, hypertension, and creatinine increase were based on the CTCAE version 4.0.

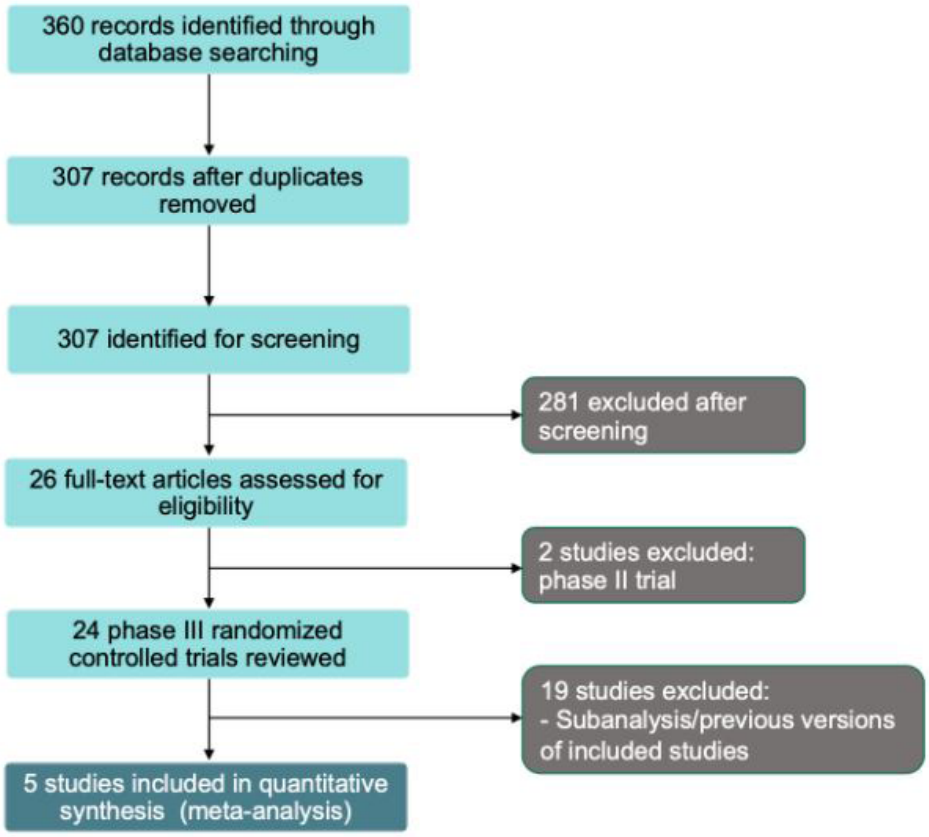

Figure 1: Flow Diagram of identification, inclusion and exclusion of studies for meta-analysis.

Study	Total N	ICI COMBO (AE´S n)	CONTROL (AE´S n)	ICI-TKI increased AST (%)	ICI-TKI increased ALT (%)	TKI increased AST (%)	TKI increased ALT (%)	ICI-TKI Hypothy (%)	TKI Hypothy (%)	ICI-TKI Diarrhea (%)	TKI Diarrhea (%)	ICI-TKI Rash (%)	TKI Rash (%)	ICI-TKI Hypertension (%)	TKI Hypertension (%)	ICI-TKI Creatinine (%)	TKI Creatinine (%)
CHECKMATE 214: Extended FU of E&S Motzer RJ et al, 2019	1096	nivolumab + ipilimumab (547)	sunitinib (535)	AG: 59(10.8) HG:20(3.7)	AG: 61(11.2) HG: 28(5.1)	AG: 51(9.5) HG: 7(1.3)	AG: 51(9.5) HG: 9(1.7)	AG: 87(15.9) HG: 2(0.4)	AG: 138(25.8) HG: 1(0.2)	AG: 133(24.3) HG: 21(3.8)	AG: 251(45.9) HG: 31(5.7)	AG: 115(21) HG: 9(1.6)	AG: 69(12.6) HG: 0(0)	AG: 12(2.2) HG: 4(0.7)	AG:216(39.5) HG: 85(15.5)	AG: 39(7.1) HG: 1(0.2)	AG: 34(6.2) HG: 2(0.4)
KEYNOTE 426 Rini B et al, 2020	861	pembrolizumab + Axitinib (429)	sunitinib (425)	AG:112(26.1) HG: 30(7)	AG: 115(26.8) HG: 57(13.3)	AG: 69(16.2) HG: 10(2.4)	AG: 64(15.1) HG: 13(3.1)	AG: 152(35.4) HG: 1(0.2)	AG: 134(31.5) HG: 1(0.2)	AG: 233(54.3) HG: 39(9.1)	AG: 191(44.5) HG: 20(4.7)	AG: 61(14.2) HG: 1(0.2)	AG: 47(10.9) HG: 2(0.5)	AG: 191(44.5) HG: 95(22.1)	AG: 193(44.9) HG: 82(19.1)	AG: 48(11.2) HG: 2(0.5)	AG: 51(11.9) HG: 3(0.7)
JAVELIN 101 Motzer RJ et al, 2019	886	Avelumab + Axitinib (434)	sunitinib (439)	AG: 63(14.5) HG: 17(3.9)	AG: 74(17.1) HG: 26(6)	AG: 52(11.8) HG: 9(2.1)	AG: 50(11.4) HG: 11(2.5)	AG: 108(24.9) HG: 1(0.2)	AG: 61(13.9) HG: 1(0.2)	AG: 270(62.2) HG: 29(6.7)	AG: 209 (48.2) HG: 12(2.8)	AG: 62(14.3) HG: 2(0.5)	AG: 49(11.3) HG: 2(0.5)	AG: 215(2.3) HG: 111(25.6)	AG: 158(36.4) HG: 75(17.3)	AG: * HG: *	AG:* HG:*
CHECKMATE 9ER Choueiri T et al, 2021	651	Nivolumab + cabozantinib (320)	sunitinib (320)	AG: 81(25.3) HG: 11(3.4)	AG: 90(28.1) HG: 17(5.3)	AG: 35(10.9) HG: 4(1.2)	AG: 27(8.4) HG: 7(2.2)	AG: 109(34.1) HG: 1(0.3)	AG: 94(29.4) HG: 1(0.3)	AG: 204(75) HG: 151(47.2)	AG: 22(6.9) HG: 14(4.4)	AG: 69(21.6) HG: 6(1.88)	AG: 26(8.1) HG: 0(0)	AG: 111(34.7) HG: 40(12.5)	AG: 119((37.2) HG: 42(13.1)	AG: 42(13.1) HG: 4(1.25)	AG: 43(13.4) HG: 1(0.3)
CLEAR Motzer RJ et al, 2021	1069*	Pembrolizumab + Lenvatinib (352)	sunitinib (340)	AG: 33(9.4) HG: 9(2.6)	AG: 34(9.7) HG: 11(3.1)	AG: 30(8.8) HG: 2(0.6)	AG: 30(8.8) HG: 6(1.8)	AG: 166(47.2) HG: 5(1.5)	AG: 90(26.5) HG: 0(0)	AG: 216(61.4) HG: 34(9.7)	AG: 168(47.7) HG: 18(5.1)	AG: 96(27.3) HG: 13(3.7)	AG: 47(13.4) HG: 2(0.6)	AG: 195(55.4) HG: 97(27.6)	AG: 141(40.1) HG: 64(18.2)	AG: 48(13.6) HG: 4(1.1)	AG: 34(9.7) HG: 2(0.6)
*JAVELIN 101 did not report creatinine alteration data AE: adverse effect, ICI: immune checkpoint inhibitor, TKI: tyrosine kinase inhibitor, AST: aspartate aminotransferase, ALT: alanine aminotransferase, AG: any-grade, HG: high-grade																	

Table 1: Characteristics and incidences of different toxicities among studied trials.

Incidence of any grade and high-grade alterations in common clinical parameters with ICI combination therapy

All studies included in the meta-analysis reported any-grade and high-grade transaminases (AST and ALT) elevation, hypothyroidism, diarrhea, rash, hypertension, and creatinine increase data in the study adverse effect profile. Tables 1 and 2 show a complete description of global and particular incidences, and other study characteristics.

Selected toxicities	No. trials	No. events	Incidence, % (95% CI)
Any-grade			
AST alteration	5	348/2082	16.71 (15.08; 18.34)
ALT alteration	5	374/2082	17.96 (16.29; 19.64)
Hypothyroidism	5	622/2082	29.88 (27.89; 31.87)
Diarrhea	5	1056/2082	50.72 (48.55; 52.89)
Rash	5	403/2082	19.35 (17.64; 21.08)
Hypertension	5	724/2082	34.77 (32.71; 36.84)
Creatinine alteration	5	177/1648	10.74 (9.22; 12.27)
High-grade			
AST alteration	5	87/2082	4.18 (3.30; 5.06)
ALT alteration	5	139/2082	6.68 (5.58; 7.77)
Hypothyroidism	5	10/2082	0.48 (0.16; 0.80)
Diarrhea	5	274/2082	13.16 (11.68; 14.64)
Rash	5	31/2082	1.49 (0.95; 2.03)
Hypertension	5	347/2082	16.67 (15.04; 18.29)
Creatinine alteration	5	11/1648	0.67 (0.24; 1.09)

ICI: Immune checkpoint inhibitor, mRCC: metastatic renal cell carcinoma, AST: aspartate aminotransferase, ALT: alanine aminotransferase

Table 2: Incidence of any-grade and high-grade selected toxicities of ICI combination therapy in mRCC patients.

Odds of any grade and high-grade alterations

Random and fixed effect models were used to calculate the summary odd ratios (OR) of any-grade and high-grade alterations of the studied variables. Table 3 shows estimates and OR with corresponding CI and p-values of the proposed analysis.

		TRANSAMINASE		HYPOTHYROIDISM		DIARRHEA		RASH		HYPERTENSION		CREATININE	
Comparison	**Trials Compared**	**Toxicity**	**Effect estimate** **OR (95%CI) ,p value**	**Toxicity**	**Effect estimate** **OR (95%CI), p-value**	**Toxicity**	**Effect estimate** **OR (95%CI), p-value**	**Toxicity**	**Effect estimate** **OR (95%CI), p-value**	**Toxicity**	**Effect estimate** **OR (95%CI), p-value**	**Toxicity**	**Effect estimate** **OR (95%CI), p-value**
ICI combination therapy versus sunitinib	**CHECKMATE 214, KEYNOTE 426, JAVELIN 101, CHECKMATE 9ER, CLEAR**	**Any grade AST alteration**	OR=1.52 (1.09-2.13), p=0.01	**Any grade Hypothyroidism**	NS	**Any grade Diarrhea**	NS	**Any grade Rash**	OR=1.85 (1.37-2.50), p<0.001	**Any grade Hypertension**	NS	**Any grade Creatinine**	NS
		High grade AST alteration	OR=2.78 (1.84-4.19), p<0.001										
		Any grade ALT alteration	OR=1.79 (1.13-2.84), p=0.01	**High grade Hypothyroidism**	NS	**High grade Diarrhea**	NS	**High grade Rash**	OR=4.56 (2.01-10.34), p<0.001	**High grade Hypertension**	NS	**High grade Creatinine**	NS
		High grade ALT alteration	OR=3.15 (2.25-4.43), p<0.001										
Double ICI versus ICI-TKI	**CHECKMATE 214 versus KEYNOTE 426, JAVELIN 101, CHECKMATE 9ER, CLEAR**	**Any grade AST alteration**	NS	**Any grade Hypothyroidism**	OR ICI-ICI=0.54 (0.40-0.73) OR ICI-TKI=1.65 (1.15-2.37) p<0.001	**Any grade Diarrhea**	OR ICI-ICI=0.36 (0.28-0.47) OR ICI-TKI=3.14 (0.85-11.57) p<0.001	**Any grade Rash**	NS	**Any grade Hypertension**	OR ICI-ICI=0.03 (0.02-0.06) OR ICI-TKI=1.28 (0.89-1.83) p<0.001	**Any grade Cretainine**	NS
		High grade AST alteration	NS										
		Any grade ALT alteration	NS	**High grade Hypothyroidism**	NS	**High grade Diarrhea**	OR ICI-ICI=0.65 (0.37-1.14) OR ICI-TKI=3.73 (1.25-11.17) p=0.01	**High grade Rash**	NS	**High grade Hypertension**	OR ICI-ICI=0.04 (0.01-0.11) OR ICI-TKI=1.36 (1.07-1.74) P<0.001	**High grade Creatinine**	NS
		High grade ALT alteration	NS										

AntiPD-1 ICI-TKI ***versus*** ***Anti PD-L1-TKI*** ***versus*** ***Anti PD-L1-Anti-CTLA-4***	**KEYNOTE 426, CHECKMATE 9ER,** **CLEAR** **versus** **JAVELIN 101** **versus** **CHECKMATE 214**	**Any grade AST alteration**	NS	**Any grade Hypothyroidism**	OR PD1-TKI=1.54 (0.97-2.45) OR PDL1-TKI=2.05 (1.45-2.09) OR PD1-CTLA4=0.54 (0.40-0.73) p<0.001	**Any grade Diarrhea**	OR PD1-TKI=3.80 (0.64-22.54) OR PDL1-TKI=1.81 (1.38-2.37) OR PD1-CTLA4=0.36 (0.28-0.47) p<0.001	**Any grade Rash**	NS	**Any grade Hypertension**	OR PD1-TKI=1.15 (0.76-1.74) OR PDL1-TKI=1.75 (1.33-2.29) OR PD1-CTLA4=0.03 (0.02-0.06) p<0.001	*	*
		High grade AST alteration	NS										
		Any grade ALT alteration	NS	**High grade Hypothyroidism**	NS	**High grade Diarrhea**	OR PD1-TKI=4.23 (0.94-18.93) OR PDL1-TKI=2.55 (1.28-5.06) OR PD1-CTLA4=0.65 (0.37-1.14) p<0.001	**High grade Rash**	NS	**High grade Hypertension**	OR PD1-TKI=1.26 (0.93-1.69) OR PDL1-TKI=1.67 (1.20-2.32) OR PD1-CTLA4=0.04 (0.01-0.11) p<0.001	*	*
		High grade ALT alteration	NS										

P values below 0.05 were deemed statistically significant

*JAVELIN 101 did not report creatinine alteration data

NS: Not significant, ICI: immune checkpoint inhibitor, TKI: tyrosine kinase inhibitor, CTLA4: cytotoxic T lymphocyte associated antigen 4, AST: aspartate aminotransferase, ALT: alanine aminotransferase, AG: any-grade, HG: high-grade, OR: odd ratio

Table 3: Estimates and OR with their corresponding CI and p values of different trial comparisons.

Hepatotoxicity

ICI combination therapy versus sunitinib

Summary ORs for any-grade and high-grade transaminase elevations were significantly higher for the combination in the case of AST (any-grade OR: 1.52 (1.09-2.13), p=0.01; high-grade OR: 2.78 (1.84-4.19), p<0.001) and ALT (any-grade OR: 1.79 (1.13-2.84), p=0.01; and high-grade OR: 3.15 (2.25-4.43), p<0.001) compared to sunitinib alone (Figure 2 A-D, Table 3).

OR according to ICI combination strategy

We analyzed the odd ratios of AST and ALT alterations with ICI combination therapy compared to sunitinib, according to the type of ICI combination: double ICI versus ICI-TKI. No significant differences in the OR of developing any-grade and high-grade AST alterations were seen between double ICI and ICI-TKI combinations. Similarly, for ALT, no significant differences in the OR of developing any-grade and high-grade ALT alterations were seen between double ICI and ICI-TKI combinations (Table 3).

There were no significant differences in any-grade and high-grade ORs of both AST and ALT parameters according to the ICI agent used (group 1: anti-PD1, group 2: anti-PD-L1, and group 3: anti-PD1+anti-CTLA-4) (Table 3).

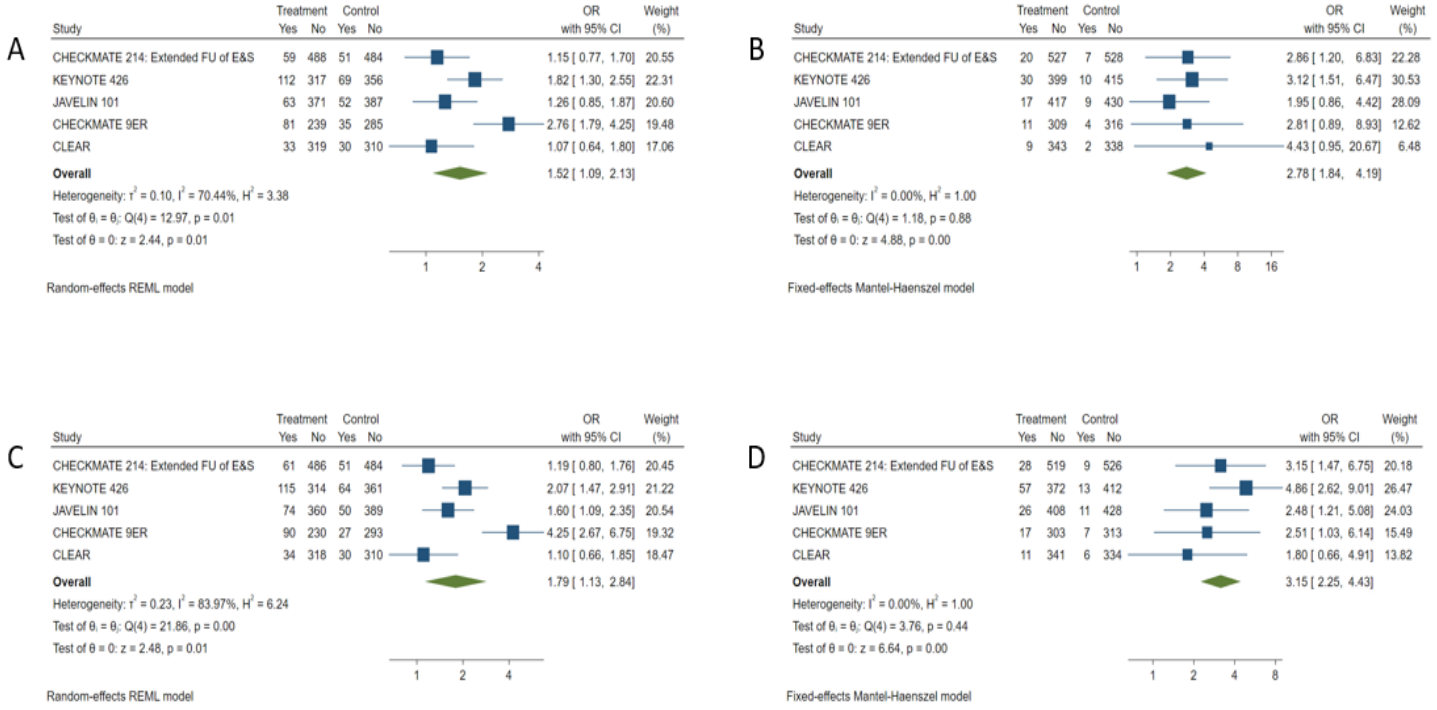

Figure 2: Forest plot of random-effects model showing odd ratios and 95% confidence intervals of any-grade AST alterations with ICI combination therapy compared to sunitinib monotherapy (A). Forest plot of fixed-effects model showing odd ratios and 95% confidence intervals of high-grade AST alterations with ICI combination therapy compared to sunitinib monotherapy (B). Forest plot of random-effects model showing odd ratios and 95% confidence intervals of any-grade ALT alterations with ICI combination therapy compared to sunitinib monotherapy (C). Forest plot of fixed-effects model showing odd ratios and 95% confidence intervals of high-grade ALT alterations with ICI combination therapy compared to sunitinib monotherapy (D).

Hypothyroidism

ICI combination therapy versus sunitinib

Summary ORs for any-grade and high-grade hypothyroidism were not significantly higher in the combination strategy compared to sunitinib alone (any-grade OR: 1.32, p=0.29, high-grade OR: 2.30, p=0.14) (Supplementary Figure 1 A-B, Table 3).

OR according to ICI combination strategy

Odds of hypothyroidism with ICI combination therapy compared to sunitinib, according to the type of ICI combination: double ICI versus ICI-TKI, were lower for developing any-grade hypothyroidism for double ICI combinations (OR double ICI: 0.54 (0.40-0.73), and higher for ICI-TKI combinations (OR ICI-TKI: 1.65 (1.15-2.37); p<0.001). There were no differences in the OR of developing high-grade hypothyroidism between double ICI and ICI-TKI combinations (Supplementary Figure 1 C-D, Table 3).

There were significant differences in the ORs of any-grade hyperthyroidism according to the ICI agent used (group 1: anti-PD1, group 2: anti-PD-L1, and group 3: anti-PD1+anti-CTLA-4), with double ICI combinations displaying the lowest OR and anti-PDL1-TKI combinations displaying the highest OR (group 1 OR: 1.54 (0.97-2.47), group 2 OR: 2.05 (1.45-2.90) and group 3 OR: 0.54 (0.40-0.73), p<0.001). On the contrary, no significant differences were found in the OR of high-grade hyperthyroidism according to the ICI agent used (Supplementary Figure 1 E-F, Table 3).

Diarrhea

ICI combination therapy versus sunitinib

Summary ORs for any-grade and high-grade diarrhea, were not significantly higher in the combination strategy, compared to sunitinib alone (any-grade OR: 2.04 (0.55-7.63), p=0.29; high-grade OR: 2.63 (0.88-7.82) p=0.08) (Supplementary Figure 2 A-B, Table 3).

OR according to ICI combination strategy

Odds of diarrhea with ICI combination therapy compared to sunitinib, according to the type of ICI combination: double ICI versus ICI-TKI, were significantly different for developing any-grade diarrhea between double ICI and ICI-TKI combinations, with significantly lower and higher odds for double ICI, and ICI-TKI combinations, respectively (OR double-ICI: 0.54(0.40-0.73); OR ICI-TKI: 1.65 (1.15-2.37); p<0.001). Significant OR differences were also found in the case of high-grade diarrhea (OR double ICI: 0.65(0.37-1.14); OR ICI-TKI: 3.73 (1.25-11.17); p=0.01) (Supplementary Figure 2 C-D, Table 3)

There were significant differences in the OR of any-grade and high-grade diarrhea according to the ICI agent used (group 1: anti-PD1, group 2: anti-PD-L1, and group 3: anti-PD1+anti-CTLA-4) with double ICI combination (Nivolumab-Ipilimumab) displaying the lowest OR in both analyses (Supplementary Figure 2 E-F, Table 3).

Rash

ICI combination therapy versus sunitinib

Summary ORs for any-grade and high-grade rash were significantly higher in the combination strategy compared to sunitinib alone (any-grade OR: 1.85 (1.37-2.50), p<0.001; high-grade OR: 4.56 (2.01-10.34) p<0.001) (Figure 3 A-B, Table 3).

OR according to ICI combination strategy

Regarding odds of rash with ICI combination therapy compared to sunitinib, according to the type of ICI combination: double ICI versus ICI-TKI. There were no significant differences in the ORs for developing any-grade or high-grade rash between double ICI and ICI-TKI combinations (Table 3)

We found no significant differences in the ORs of any-grade and high-grade rash according to the ICI agent used (group 1: anti-PD1, group 2: anti-PD-L1, and group 3: anti-PD1+anti-CTLA-4) (Table 3).

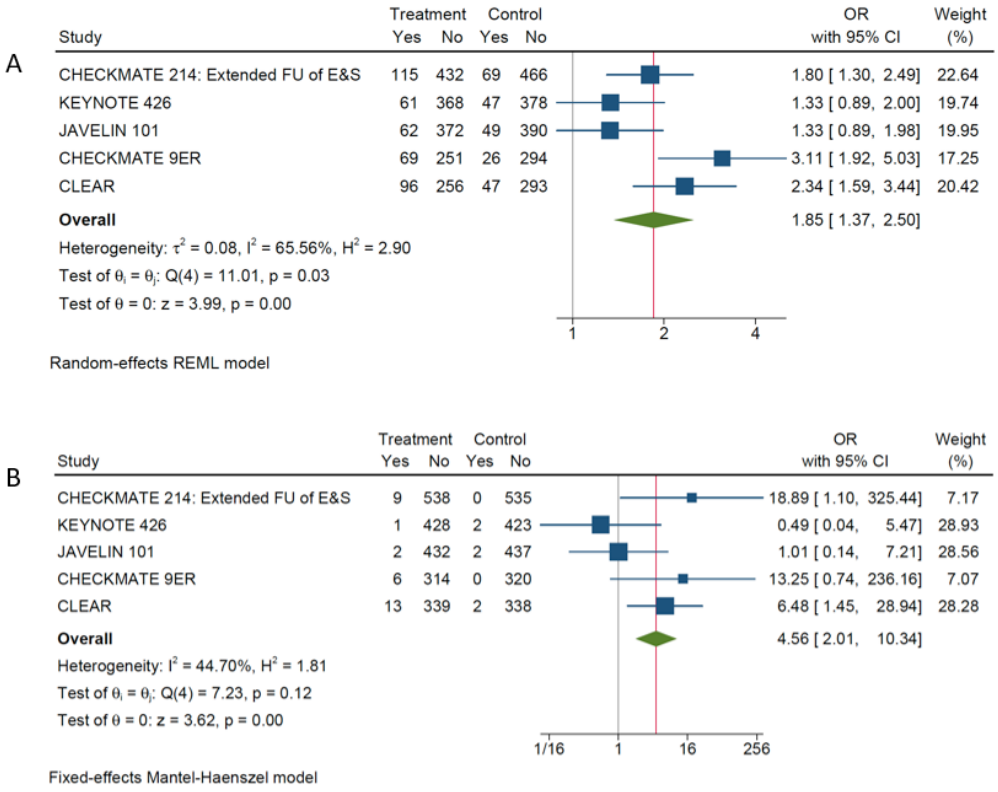

Figure 3: Forest plot of random-effects model showing odd ratios and 95% confidence intervals of any-grade rash with ICI combination therapy compared to sunitinib monotherapy (A). Forest plot of fixed-effects model showing odd ratios and 95% confidence intervals of high-grade rash with ICI combination therapy compared to sunitinib monotherapy (B).

Hypertension

ICI combination therapy versus sunitinib

ORs for any-grade and high-grade hypertension, were not significantly different in the combination strategy, compared to sunitinib alone (any-grade OR: 0.62 (0.15-2.62), p=0.52; high-grade OR: 0.69 (0.18-2.58), p=0.58) (Supplementary Figure 3 A-B, Table 3).

OR according to ICI combination strategy

Regarding the odds of hypertension with ICI combination therapy compared to sunitinib, according to the type of ICI combination: double ICI versus ICI-TKI; there were significant differences in the OR for developing any-grade hypertension between double ICI and ICI-TKI combinations, with lower odds in the double ICI group (OR double ICI: 0.03 (0.02-0.06); OR ICI-TKI: 1.28 (0.89-1.83); p<0.001). Significant differences and trends were also found in the case of high-grade hypertension: OR double ICI: 0.04 (0.01-0.11); OR ICI-TKI: 1.36 (1.07-1.74); p<0.001) (Supplementary Figure 3 C-D, Table 3).

There were also significant differences in the OR of any-grade and high-grade hypertension according to the ICI agent used (group 1: anti-PD1, group 2: anti-PD-L1, and group 3: anti-PD1+anti-CTLA-4). With double ICI combination (anti-PD1+anti-CTLA-4) presenting the lowest OR in both analysis (any-grade OR: 0.03 (0.02-0.06); high-grade OR: 0.04 (0.01-0.11)) (Supplementary Figure 3 E-F, Table 3).

Creatinine

ICI combination therapy versus sunitinib

ORs for any-grade and high-grade creatinine increase, were not significantly different in the combination strategy, compared to sunitinib alone (any-grade OR: 1.09 (0.87-1.36), p=0.48; high-grade OR: 1.35 (0.54-3.37), p=0.52) (Supplementary Figure 4 A-B, Table 3).

OR according to ICI combination strategy

Regarding the odds of creatinine increase with ICI combination therapy compared to sunitinib, according to the type of ICI combination: double ICI versus ICI-TKI. There were no

significant differences in the OR of any-grade creatinine increase between double ICI and ICI-TKI combinations (OR double ICI: 1.13 (0.70-1.82); OR ICI-TKI: 1.07 (0.83-1.39); p=0.85). Also, no significant OR differences were found in the case of high-grade creatinine increase: OR double ICI: 0.49 (0.04-5.40); OR ICI-TKI: 1.65 (0.60-4.54); p=0.36) (Table 3).

Study Quality and Publication Bias

Funnel plots were used to estimate the publication bias of the OR of any-grade and high-grade AST and ALT alterations, hypothyroidism, diarrhea, rash, hypertension, and creatinine increase. The test and symmetry of the funnel plots suggested no evidence of publication bias for the OR of any grade and high-grade AST and ALT alterations (Egger's test p-value >0.1).

The risk of bias of individual studies is presented in Supplementary Figure 5

Discussion

To our knowledge, we report the first analysis evaluating the risk of selected key adverse events commonly encountered in clinical practice (hepatotoxicity, hypothyroidism, diarrhea, rash, hypertension, and creatinine increase) associated with ICI combination therapy, including double ICI and ICI-TKI combinations, compared to sunitinib monotherapy in mRCC. Many of these adverse events can be induced by both drug families (ICI and TKI) through different mechanisms [10,15,16]. Thus, we hypothesized that the use of anti-PD1/PD-L1 in combination with an anti-CTLA-4 or with a TKI would translate into an increased risk of these selected adverse events. Our analysis included 4726 patients from five randomized clinical trials using FDA-approved ICI-combination therapies (nivolumab-ipilimumab, pembrolizumab-axitinib, nivolumab-cabozantinib, pembrolizumab-lenvatinib, and avelumab-axitinib) [4-8]. Sunitinib was the control arm in all trials. Our study showed that the use of ICI combination therapy, either double ICI or ICI-TKI, compared to sunitinib, significantly increases the risk of developing any-grade and high-grade hepatotoxicity and rash.

Hepatotoxicity has been broadly described in both ICI and TKI therapies; however, little is known about the potential summed toxicity of ICI-TKI combinations. Reporting and interpreting the incidence of hepatotoxicity in clinical trials is challenging given the lack of a systematic way to report it and the possibility of using multiple analytical parameters to describe it (i.e., AST, ALT, or bilirubin alterations). This becomes more difficult in the current mRCC scenario of ICI combination therapies, as both ICI and TKI can induce hepatotoxicity through different mechanisms [15-21]. According to two large meta-analyses, the incidence of any-grade and high-grade AST and ALT alterations in patients receiving ICI therapy is around 5% and 1.5%, with a RR of any-grade and high-grade hepatotoxicity of 1.80 and 2.79, respectively compared to non-ICI therapy [17,19]. Regarding tyrosine-kinase inhibitors, several studies, conducted across solid tumors and specifically RCC, have reported an incidence of TKI-associated hepatotoxicity of around 37% and 5% for any-grade and high-grade toxicity, respectively [22]. however, results are often conflicting and variable, with a large meta-analysis including 18,292 patients from 52 trials showing a lower incidence of both any-grade (8%) and high-grade (1.4%) hepatotoxicity [18]. On the other side, pivotal trials of ICI combination therapy in mRCC, with either double ICI or ICI-TKI combinations, have reported a higher incidence of liver toxicity with ICI combination than that reported above (ranging from 10-35% for any-grade, and from 3-13% for high-grade toxicity) [4–8]. This was confirmed for ICI-TKI combinations in a recent meta-analysis by Rizzo and colleagues [23]. In our analysis, any grade and high-grade hepatotoxicity incidence was relatively low, although above that reported with single-agent ICI or TKI [17,22]. In line with previously reported results, ICI combination therapy, including double ICI, was associated with a higher risk of hepatotoxicity compared to sunitinib monotherapy. The increase in the OR of hepatotoxicity was notably higher for severe hepatotoxicity (nearly three times higher with the combinations). The type of ICI combination, either double ICI versus ICI-TKI and the type of ICI agent used (i.e., anti-PD vs. anti-PD-L1 vs. anti-CTLA4), did not have a significant impact on the risk of hepatotoxicity. These results confirm the increased risk of toxicity with combination therapies and showcase the paradigm of the difficulty discerning the agent responsible for the toxicity, further complicating its management.

Our analysis also revealed a 1.9 and 4.6-fold increased risk of any grade and high-grade rash, respectively, in patients treated with ICI combination therapy compared to those treated with sunitinib monotherapy. A similar increased risk in any-grade rash was observed in a previous meta-analysis across solid tumors (2-fold) treated with ICI therapy; however, in contrast to our results, no significant differences in the risk of high-grade rash were seen [19]. Such differences could be partially explained by the fact that such meta-analysis mainly included single-agent ICI therapies. Our results also differ from those reported by Rizzo et al., who did not find significant differences in the risk of rash between ICI-TKI combinations and sunitinib [23]. This could be explained by the fact that in our analysis, rash toxicity was mainly driven by the double ICI group, not included in their meta-analysis. Although skin toxicity is often perceived as a minor toxicity, our results show a significantly increased risk of severe skin toxicity with ICI combination therapy, underscoring the importance of early recognition and management of potentially life-threatening skin toxicities. In addition, no significant differences were observed in the risk of developing hypothyroidism, diarrhea, hypertension, and creatinine increase between patients treated with ICI combination therapy and those treated with sunitinib monotherapy. However,

the risk of any-grade hypothyroidism and any-grade and high-grade diarrhea and hypertension were significantly higher with ICI-TKI combinations than with double ICI, highlighting the added toxicity mechanisms of both drugs and the potential role of TKIs as the primary driver of such toxicities.

This study has several limitations. First, this meta-analysis was based on study-patient data rather than individual patient data, which would limit the power of our analysis. In this line, and as a second limitation, potentially hepatotoxic co-mediators, comorbidities, and the presence of liver metastases, a common site of disease dissemination that can derive in liver function test alterations, could act as a potential confounding factor. Third, liver toxicity is usually reported in clinical trials as ALT and AST, among other alterations, such as bilirubin, alkaline phosphatase, and gamma-glutamyl transferase; however, our study only evaluated ALT/AST alterations. In fact, out of the five studies included in this meta-analysis, only the Checkmate 214 and the Checkmate9ER reported other LFT than AST/ALT alterations; however, such information was not considered for the analysis. Similarly, nephrotoxicity is frequently multifactorial and can be reported not only as creatinine elevation but also as glomerular filtration rate or proteinuria, which could somehow divert our conclusions if considered for analysis. Fourth, the Immotion151 trial was excluded from the meta-analysis due to discrepancies in how hepatotoxicity was reported. On the contrary, although not included in ESMO guidelines, we have included Javelin-101 results in the metanalysis given that such combination is an added treatment option according to NCCN guidelines, and its inclusion broadens the analysis of possible ICI-TKI interactions. Finally, although increased risk toxicity with combined therapy was proven, the exact pathogenesis of the synergistic and additive mechanisms underlying overlapping toxicities under ICI-TKI combination therapies goes beyond the main scope of the present analysis and so remains to be clarified.

In conclusion, this meta-analysis confirms that ICI combination therapies, including double ICI and ICI-TKI, are associated with a significant increase in the incidence and risk of developing hepatotoxicity and rash compared to sunitinib monotherapy in mRCC. In addition, the type of ICI combination strategy used, double ICI or ICI-TKI, and the type of immune checkpoint inhibitor used (anti-PD1, anti-PDL1, or anti-PD1 + anti-CTLA 4) do not seem to impact the risk of these two toxicities. However, it should be noted that ICI-TKI combinations compared to double ICI are associated with an increased risk of any-grade and high-grade hypothyroidism, diarrhea, and hypertension. These findings highlight the importance of active monitoring and early recognition and management of potentially life-threatening toxicities. Based on our results, treatment selection for mRCC patients in first-line setting should be guided by the potential toxicity profile as well as the patient's comorbidities. Further studies are needed to better understand the underlying synergistic and additive mechanisms of shared adverse events with ICI combination therapy and to identify predictive markers to avoid severe toxicity and consequent treatment discontinuation.

Statements and Declarations

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Informed Consent Statement:

Not applicable.

Competing Interests:

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Author Contributions:

Lucia Carril Ajuria, Santiago Teran and Guillermo de Velasco, contributed to the conception and design of the study. Data collection, analysis and interpretation were performed by Lucia Carril Ajuria, Santiago Teran and David Lora. Lucía Carril Ajuria and Santiago Teran drafted the manuscript. Critical revision of the manuscript for important intellectual content was performed by Lucia Carril Ajuria, Santiago Teran, Guillermo de Velasco, Ray Manneh, Maricruz Martin-Soberon, Alberto Carretero-Gonzalez, Daniel Castellano. All authors read and approved the final manuscript.

Data Availability:

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval:

Given the nature of the study, no ethics approval was required.

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