SYSTEMATIC REVIEW AND META-ANALYSIS: EFFICACY AND SAFETY OF IPILIMUMAB COMBINED WITH NIVOLUMAB VS. MONOTHERAPY FOR THE TREATMENT OF METASTATIC MELANOMA

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SUMMARY

Introduction: Immunotherapy, together with Ipilimumab and nivolumab are among the most widely used treatment options for metastatic melanoma involvement. This study compares the efficacy and safety of the combination of ipilimumab with nivolumab versus nivolumab or ipilimumab monotherapy for treating metastatic melanoma.

Methods: A systematic review was conducted by extracting information from publications from different databases. Five articles were included in the review. Progression-free survival (PFS), overall survival (OS), partial response (PR), complete response (CR), objective response rate (ORR), and adverse events (AEs) of any grade and grade 3-4 were estimated.

Results: We found superiority of combination therapy vs. ipilimumab in terms of PFS (HR 0·41, 95% CI [0·35, 0·49]), OS (HR 0·64, 95% CI [0·54, 0·77]), PR (RR 2·82, 95% CI [2·09, 3·81]), CR (RR 5·69, 95% CI [1·24, 26·04]) and ORR (RR 3·58, 95% CI [2·10, 6·11]); between combination therapy and nivolumab there was no statistically significant difference. An increased risk of grade 3-4 AEs was also found for combination therapy versus ipilimumab (RR 2·24, 95% CI [1·84, 2·72]) and nivolumab (RR 2·71, 95% CI [2·22, 3·31]); there was no statistically significant difference for AEs of any grade between combination therapy and monotherapy. The adverse events with the greatest strength of association were increased ALT (RR 4·23), increased AST (RR 3·74), and fever (RR 2·67).

Conclusions: This meta-analysis shows that nivolumab monotherapy is the best option for the treatment of metastatic melanoma. This study was done with own financing.

Keywords: melanoma, nivolumab, ipilimumab, efficacy, meta-analysis.

INTRODUCTION

Melanoma is a malignant tumor of the skin whose cells originate from melanocytes.[1] According to data reported by Globocan, cutaneous melanoma is the least frequent among the types of skin cancer (21·3%); however, it is the one that represents the highest mortality in this group of neoplasms (47·2%),[2] Its prognosis is poor, with a described survival rate of 25% in the first year after diagnosis.[3] Because of this, and since its incidence has increased in recent years, melanoma has become a matter of interest in public health.

By 2020, melanoma was among the first 20 causes of cancer in the world behind oral cavity cancer and surpassing ovarian cancer, with an incidence of 324,635 new cases per year. On the other hand, it is among the first 25 causes of death by cancer, with a mortality of 57,043 cases per year. It occurs most frequently in European countries (46·4%), North America (32·4%), and Asia (7·3%), the highest mortality rate is also found in these three regions as well, with slightly higher mortality in Asia than in North America.[2]

The distribution by genre is 1·3 times more frequent in men than in women.[2] According to GLOBOCAN, in 2020, melanoma ranked 18th among the most frequent types of cancers in Colombia, with an incidence of 1,805 cases per year, and 20th among the most frequent causes of death from cancer, with a mortality of 490 cases per year.[2] However, population statistics on this type of cancer is scarce, so there may be underreporting, with an estimated diagnosis of 102 new cases per 100,000 inhabitants per year, a figure that is increasing, making it one of the most frequent cancers in the country.[4]

The type of treatment depends on the location, genetic characteristics of the lesion, and stage of the disease. Treatment options for metastatic disease include surgical resection, chemotherapy, radiotherapy, radiosurgery, immunotherapy, and targeted therapy.[5]

In recent years, there has been a growing increase in the use of immunotherapy for the treatment of metastatic melanoma, such as antibodies that bind to programmed death receptor 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen-4 (CTL-4) expressed on the surface of T-cells, providing greater control of the disease; furthermore, in recent years multiple studies have been carried out in which the potential benefits of the combination of different immunomodulators have been described, as a result, the Food and Drug Administration (FDA) has approved the combination of PD-1 and CTL-4 in selected cases. However, since there is no clear evidence of the interaction between the molecules, no recommendation on this combination's use can be suggested yet.[6]

Therefore, the present study seeks to compare the efficacy and safety of the combination of nivolumab with ipilimumab versus nivolumab or ipilimumab in monotherapy to treat metastatic melanoma.

METHODOLOGY

Search strategy

This systematic review and meta-analysis was registered on the National Institute for Health Research (NIHR) PROSPERO website under ID CRD42022330717, having verified the information using the PRISMA (Preferred Reporting Items for Systematic Review and Metanalysis) statement checklist.

A systematic search of the literature related to the efficacy and safety of ipilimumab and nivolumab combination immune therapies for metastatic melanoma was performed using PubMed, Scopus, and Embase search engines; the search was conducted until August 2022. An additional examination of Cochrane Central and ClinicalTrials.gov was also undertaken to include unpublished clinical trials. The MeSH terms used were "melanoma [Mesh] AND (nivolumab [Mesh] AND ipilimumab [Mesh]) AND (overall survival [supplementary concept] OR OS [supplementary concept] OR progression-free survival [Mesh] OR PFS [supplementary concept] OR safety [Mesh])". The corresponding DeCS terms were "melanoma AND (nivolumab AND ipilimumab) AND (eficacia OR supervivencia global OR supervivencia sin progresión OR supervivencia sin acontecimientos OR supervivencia sin evento)".

Links of interest

The outcomes of interest considered for this study were: overall survival (OS), progression-free survival (PFS), partial response (PR), complete response (CR), objective response rate (ORR), and adverse events (AEs).

Eligibility Criteria

Articles were selected when they met the following criteria: population of men and women of any age, metastatic melanoma (stage III/IV), randomized clinical trials, articles in English or Spanish, and treatment with nivolumab and ipilimumab in monotherapy or in combination. We included articles whose results were expressed in terms of hazard ratio (HR) for overall survival and progression-free survival or risk ratios (RR) for the other outcomes.

Reviews, letters, case reports, case series, cohort or case-control studies, pregnant or lactating women, squamous cell carcinoma, basal cell carcinoma, and treatments other than nivolumab or ipilimumab administration were excluded.

Selection of studies

The Rayyan program was used for the initial management of the literature. Duplicate records were excluded, then the titles and abstracts of articles with potential relevance were reviewed, and those that did not meet the eligibility criteria were excluded; finally, a complete review of the selected texts was performed from which articles were chosen for inclusion in the study. The review of the articles was performed by 2 of the investigators (J.S. and A.P.), and cases of discrepancies between authors were resolved by a third investigator (A.R.).

Review Manager 5.4.1 was used based on Cochrane recommendations for evaluating the quality of scientific literature.

Information extraction

The following information was extracted from the selected studies: lead author, year of publication, sample size, mean age, the proportion between men and women, ECOG index, median follow-up, treatment administered, OS, PFS, PR, CR, ORR, and treatment-related AE of any grade. Because some of the articles were found to consist of follow-up reports of the same study, population characterization information from previous publications was consulted for comparisons.

The results were summarized using Review Manager 5.4.1 and Excel programs. The heterogeneity of the studies was determined with the statistic I^2, and publication bias was assessed using Begg's test and funnel plots.

RESULTS

Search and study characteristics

A total of 631 articles were obtained from the Pubmed, Embase, and Scopus databases, and 43 articles from Cochrane Central and ClinicalTrials.gov for a total of 674 documents. When duplicates were removed, 485 articles remained, of which 468 were excluded because they did not meet the inclusion criteria by examining by title and abstract, getting 17 articles.[7-22,25] 12 articles were removed for duplicate data and for including neoplasms other than the one of interest, resulting in five articles included for analysis (Figure 1).

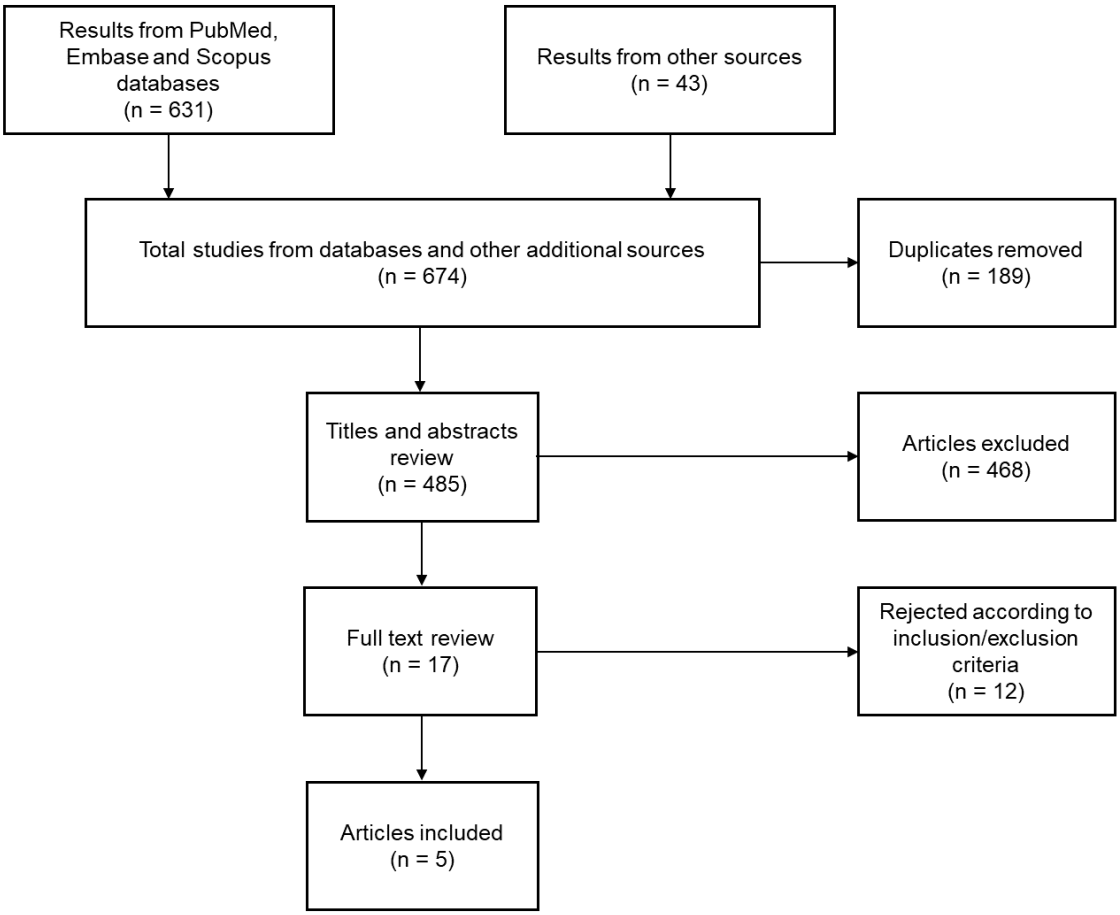

Figure 1: Flow diagram of screening and selection of studies for review. Own elaboration.

Table 1: Characterization of the population included in the meta-analysis. Own elaboration.

Study	Indicative	Age, mean (years)			Sex (male) [n (%)]			Patients (n)			Follow up, median (months)			ECOG 0 [n (%)]			Treatment	
		C	I	N	C	I	N	C	I	N	C	I	N	C	I	N	C	N
Friedman (2022)	1	56	66		9 (90)	6 (67)		10	9		12.2	12.2		7 (70)	6 (67)		Ipilimumab 3mg/kg + nivolumab 1mg/kg	Nivolumab 3mg/kg
Hodi (2016)	2	64	67		63 (66)	32 (68)		95	47		24.6	23		79 (83)	37 (79)		Ipilimumab 3mg/kg + nivolumab 1mg/kg	Nivolumab 3mg/kg
Long (2018)	3	59		63	29 (83)		19 (76)	35		25	14		17					
Wolchok (2021)	4	59	61	59	206 (65.6)	202 (64.1)	202 (63.9)	314	315	316	57.5	18.6	36	230 (73.2)	224 (71.1)	238 (75.3)	Ipilimumab 3mg/kg + nivolumab 1mg/kg	Nivolumab 3mg/kg
Zimmer (2020)	5				31 (55)		31 (53)	56		59	8		18	56 (100)		52 (88)		Nivolumab 3mg/kg

ECOG: Eastern Cooperative Oncology Group; C: Combination; I: Ipilimumab; N: Nivolumab

All trials contained a description of the randomization method. Three of the five articles were double-blinded, and all included information on missing cases. The mean age of the study subjects was between 56 and 67 years, most were male and had a baseline ECOG 0. The essential characteristics of the included studies are presented in Table 1a and 1b. The risk of bias is illustrated in Figure 2.

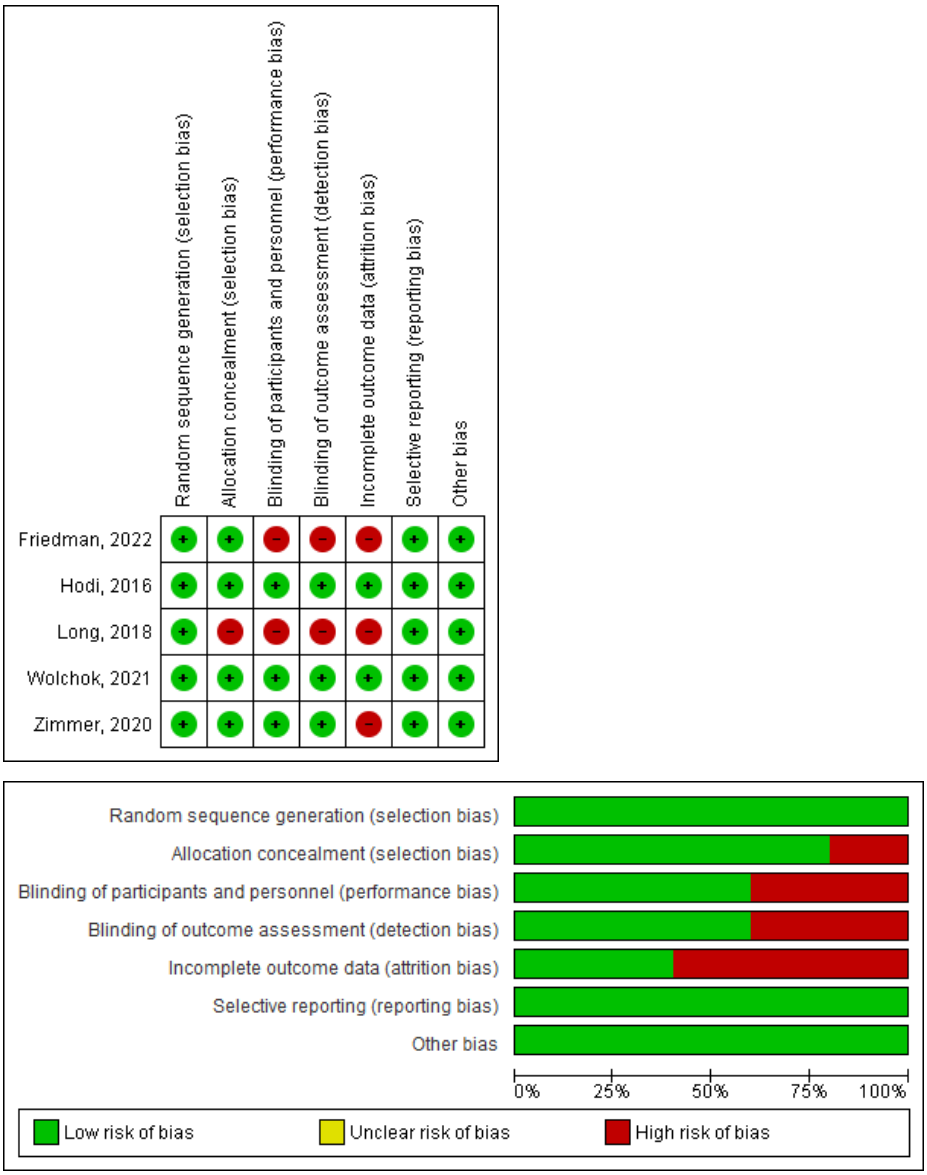

Figure 2: Risk of bias. Own elaboration.

Progression-free survival

In two of the clinical trials, a higher progression-free survival (HR = 0·41, 95% CI [0·35, 0·49]) was achieved with the combination of nivolumab and Ipilimumab compared to ipilimumab monotherapy, with no heterogeneity [p = 0·56, I^2 = 0%]. Progression-free survival was similarly superior for combination therapy at 12 months (RR = 3·13, 95% CI [2·36, 4·15]), 18 months (RR = 3·97, 95% CI [2·84, 5·54]), and 24 months (RR = 3·61, 95% CI [2·54, 5·12]) compared to Ipilimumab, with non-heterogeneity [p = 0·43, I^2 = 0%; p = 0·32, I^2 = 0%; and p = 0·86, I^2 = 0%, respectively] (Figure 3).

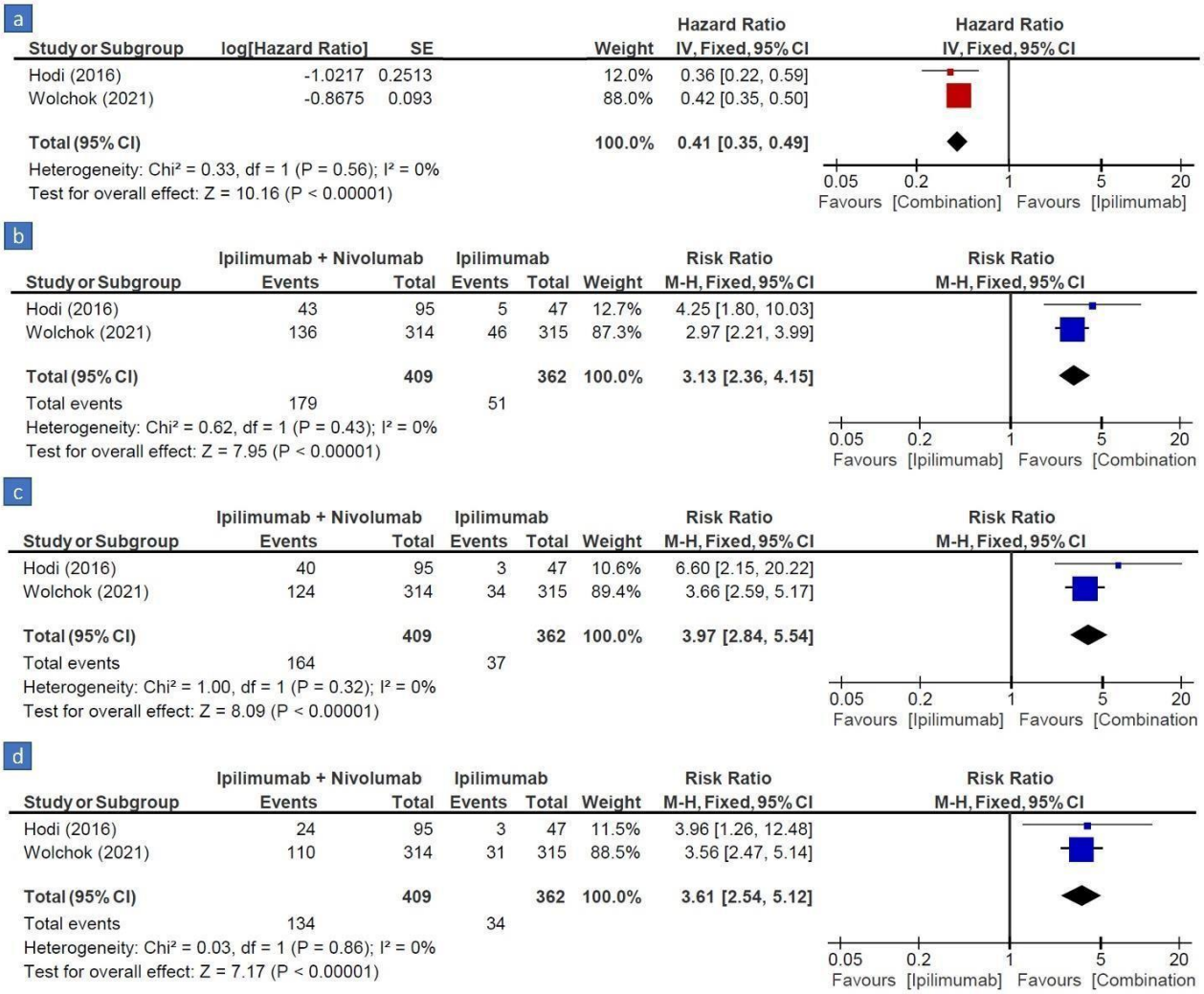

Figure 3: Forest plots for progression-free survival between ipilimumab with nivolumab and Ipilimumab alone. (a) HR of PFS. (b) PFS at 12 months. (c) PFS at 18 months. (d) PFS at 24 months. Own elaboration.

Regarding the comparison between the combined therapy and nivolumab, no statistically significant difference was found for progression-free survival (HR = 0·58, 95% CI [0·31, 1·10]) applying the random effects model for high heterogeneity [$p < 0·05$, $I^2 = 89\%$]. Similarly, there was no statistically significant difference in progression-free survival at 12 months (RR = 1·18, 95% CI [0·99, 1·39]), 18 months (RR = 1·20, 95% CI [1·00, 1·45]), and 24 months (RR = 1·14, 95% CI [0·93, 1·40]) between combination therapy and nivolumab, with no heterogeneity [$p = 0·67$, $I^2 = 0\%$; $p = 0·85$, $I^2 = 0\%$; and $p = 0·95$, $I^2 = 0\%$, respectively] (Figure 4).

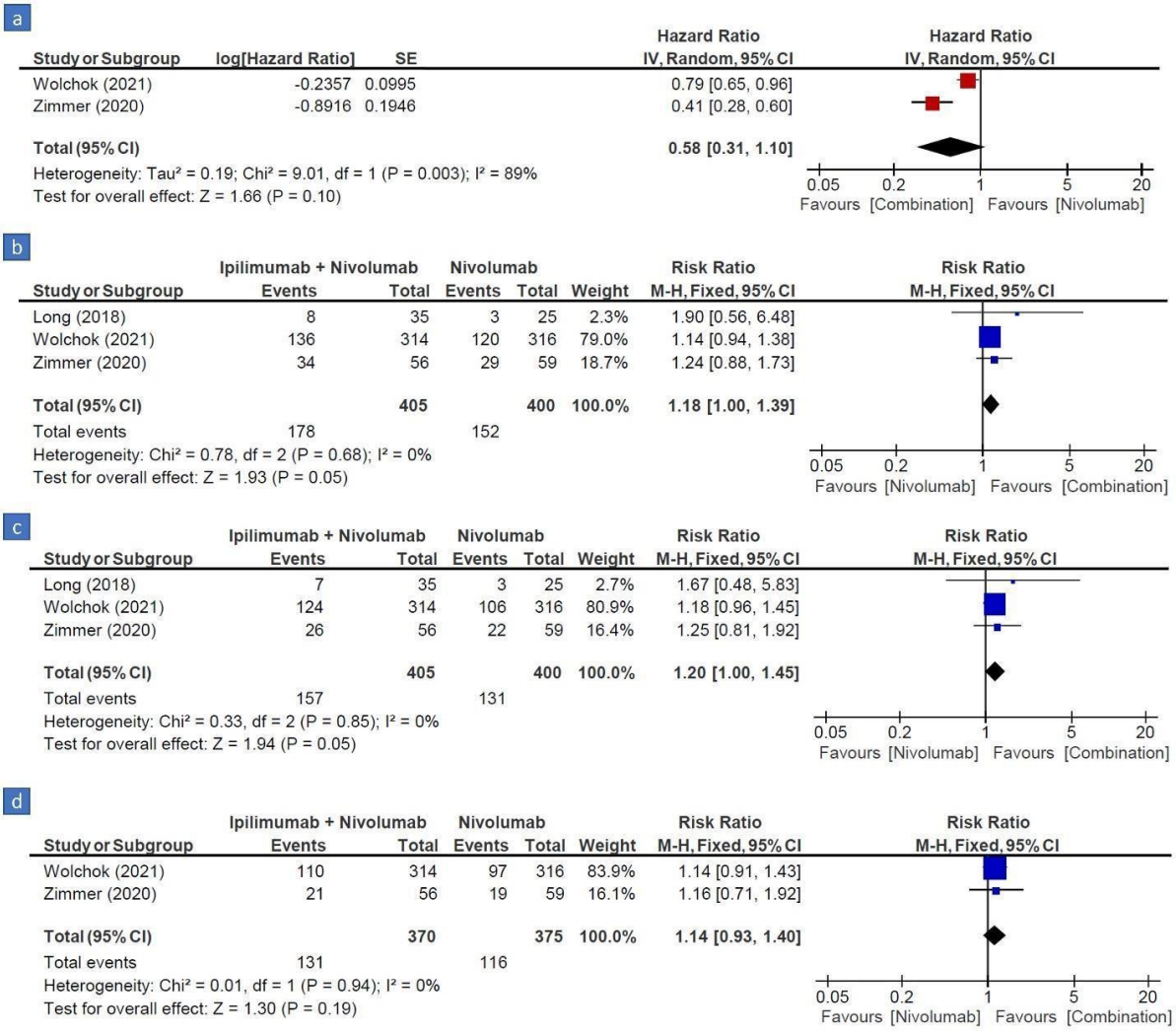

Figure 4: Forest plots for progression-free survival between ipilimumab with nivolumab and nivolumab alone. (a) HR of PFS. (b) PFS at 12 months. (c) PFS at 18 months. (d) PFS at 24 months. Own elaboration.

Overall survival

Superior overall survival (HR = 0·64, 95% CI [0·54, 0·77]) was achieved with the combination of nivolumab, and Ipilimumab compared to ipilimumab monotherapy, with no heterogeneity [p = 0·58, I^2 = 0%]. Overall survival was similarly longer for combination therapy at 12 months (RR = 1·13, 95% CI [1·02, 1·25]), 18 months (RR = 1·28, 95% CI [1·14, 1·45]), and 24 months (RR = 1·44, 95% CI [1·26, 1·66]) compared to Ipilimumab, with no heterogeneity [p = 0·73, I^2 = 0%; p = 0·79, I^2 = 0%; and p = 0·46, I^2 = 0%, respectively] (Figure 5).

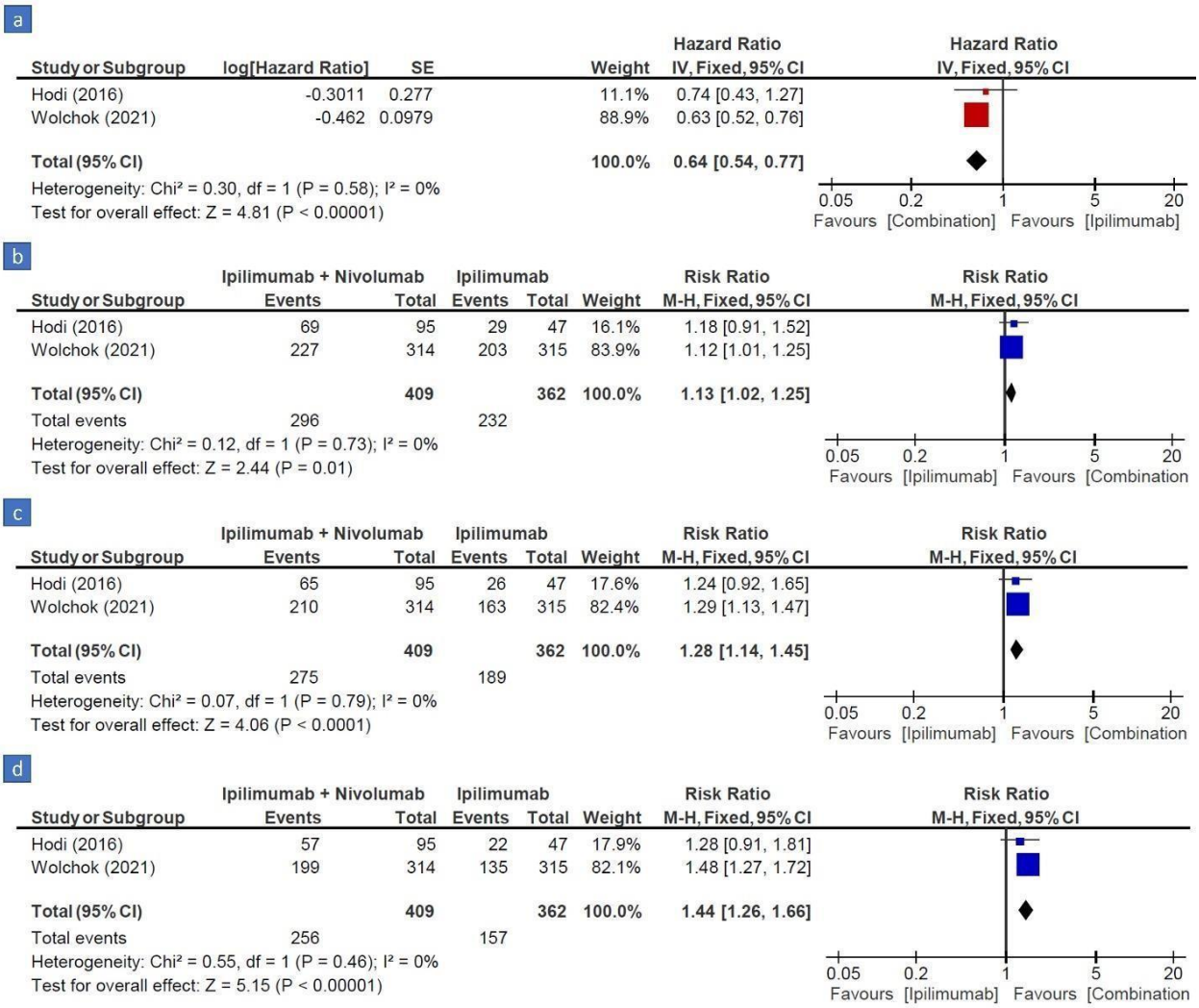

Figure 5: Forest plots for overall survival between ipilimumab with nivolumab and Ipilimumab alone. (a) HR of OS. (b) OS at 12 months. (c) OS at 18 months. (d) OS at 24 months. Own elaboration.

Between combination therapy and nivolumab monotherapy, there was no statistically significant difference in overall survival at 12 months (RR = 0·98, 95% CI [0·74, 1·30]), 18 months (RR = 1·06, 95% CI [0·95, 1·19]) and 24 months (RR = 1·11, 95% CI [0·98, 1·26]) between combined therapy and nivolumab, with no heterogeneity or moderate heterogeneity [p = 0·10, I^2 = 57%; p = 0·67, I^2 = 0%; and p = 0·98, I^2 = 0%, respectively] (Figure 6).

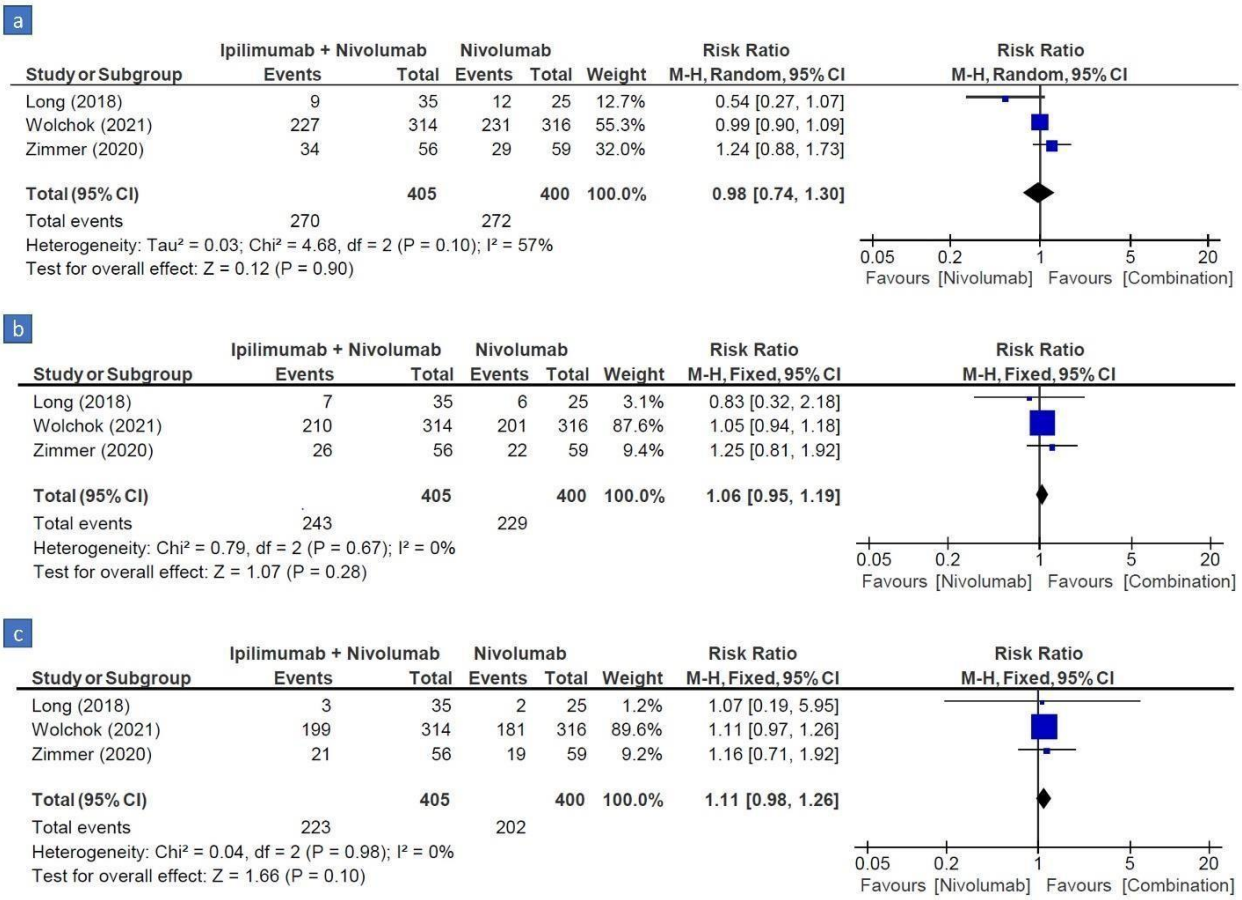

Figure 6: Forest plots for overall survival between ipilimumab with nivolumab and nivolumab alone. (a) OS at 12 months. (b) OS at 18 months. (c) OS at 24 months. Own elaboration.

Response rates

We found a higher PR for combination therapy (RR = 2·82, 95% CI [2·09, 3·81]) compared to ipilimumab monotherapy, with no heterogeneity [p = 0·61, I^2 = 0%] (Figure 7). In contrast, no statistically significant difference was found for PR between combination therapy and nivolumab (RR = 1·71, 95% CI [0·82, 3·55]), with low heterogeneity [p = 0·21, I^2 = 37%] (Figure 8).

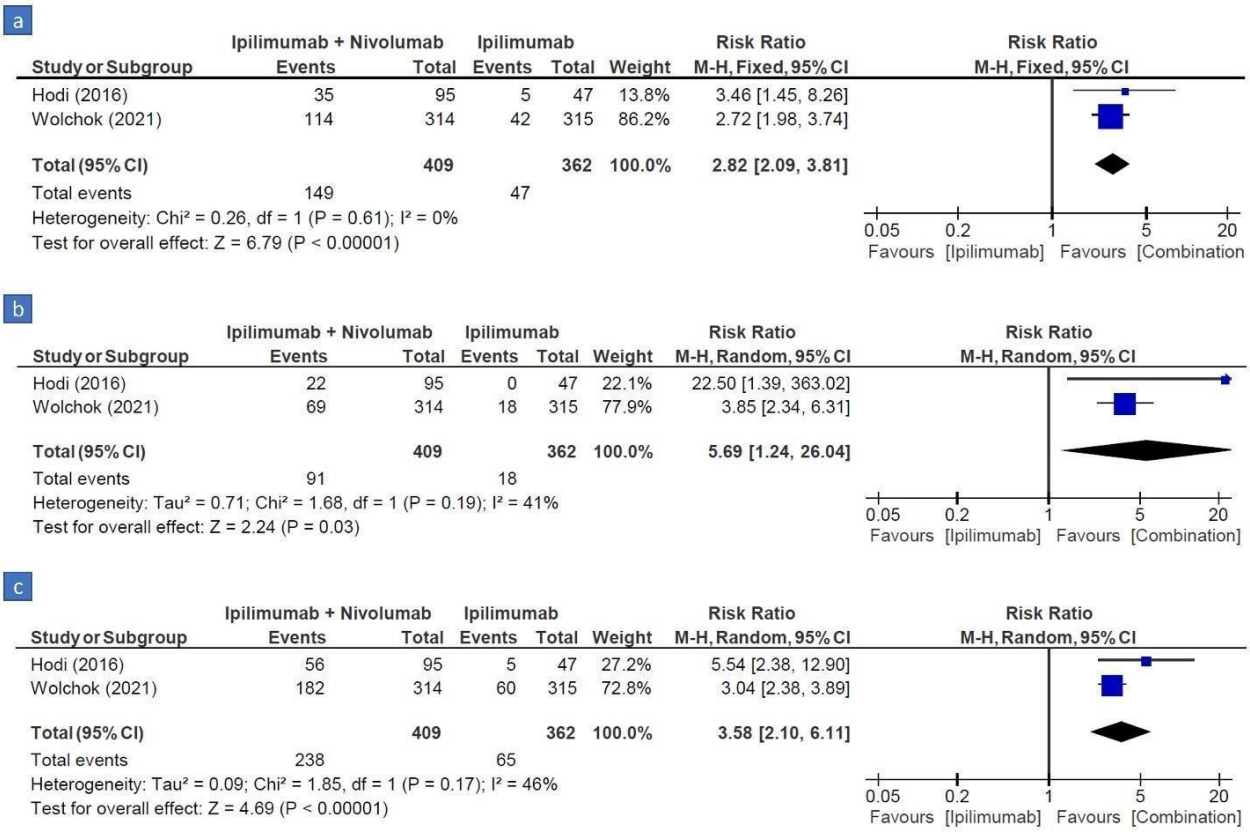

Figure 7: Forest plots for response rates between combination therapy and ipilimumab. (a) Partial response (PR). (b) Complete response (CR). (c) Objective response rate (ORR). Own elaboration.

Regarding CR, there was evidence of the superiority of combined therapy versus ipilimumab (RR = 5·69, 95% CI [1·24, 26·04]), with low heterogeneity [p = 0·19, I^2 = 41%]. However, we failed to demonstrate a statistically significant difference between combination therapy (RR = 1·17, 95% CI [0·87, 1·58]) and nivolumab monotherapy, with no heterogeneity [p = 0·76, I^2 = 0%].

In terms of ORR, the superiority of combined therapy (RR = 3·58, 95% CI [2·10, 6·11]) was observed compared to ipilimumab alone, with low heterogeneity [p = 0·17, I^2 = 46%]. However, there was no statistically significant difference vs. nivolumab (RR = 1·46, 95% CI [0·92, 2·33]), with low heterogeneity [p = 0·20, I^2 = 40% respectively].

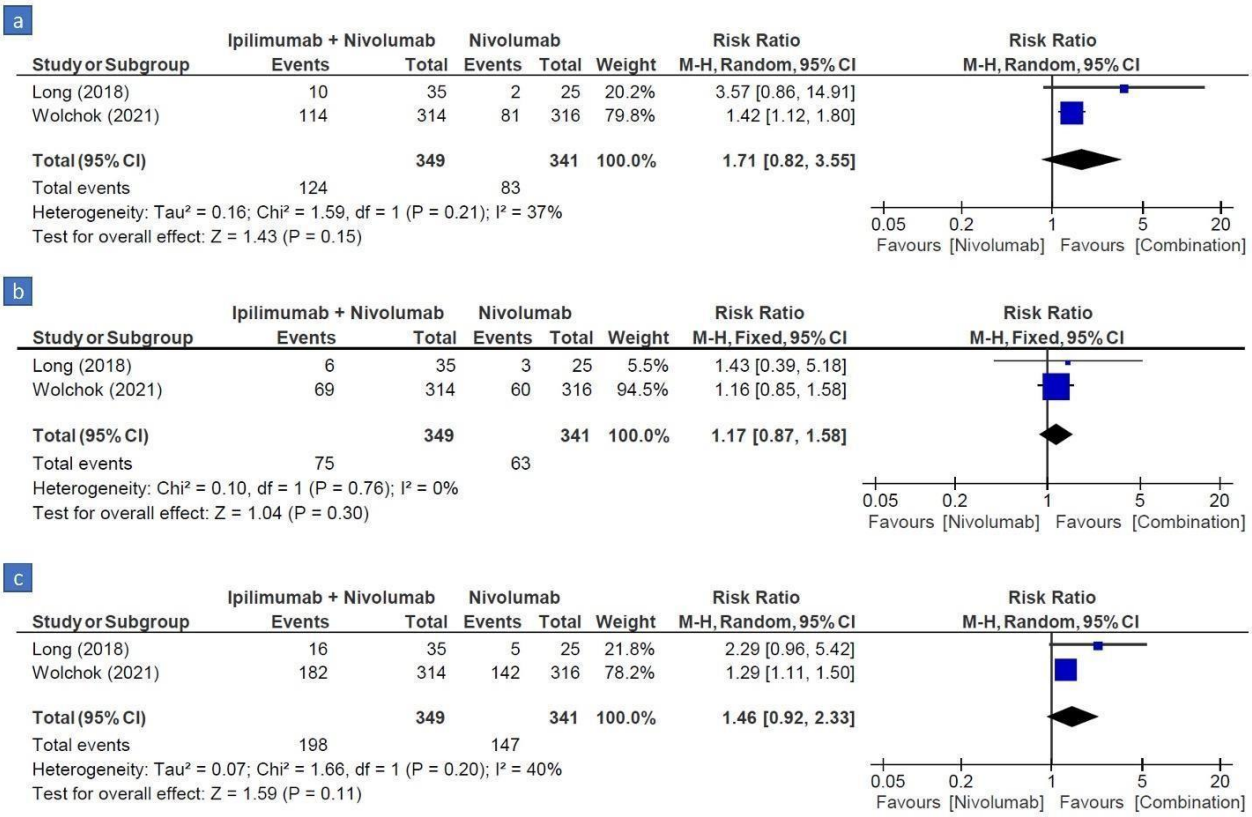

Figure 8: Forest plots for response rates between combination therapy and nivolumab. (a) Partial response (PR). (b) Complete response (CR). (c) Objective response rate (ORR). Own elaboration.

In one of the clinical trials, which was not included in the meta-analysis due to the distortion it would produce in the data analysis because of the low number of subjects included, a PR, CR, and ORR of 0% vs. 11%, 20% vs. 4% and 20% vs. 56%, respectively, were found for the combination group vs. treatment with ipilimumab as monotherapy.

Adverse events

There was no statistically significant difference in presenting any AE between combination therapy (RR = 1·06, 95% CI [0·94, 1·20]) and ipilimumab monotherapy, under the random effects model for high heterogeneity [$p < 0{\cdot}05$, $I^2 = 76\%$] (Figure 9). However, it was possible to find a higher frequency of AEs for combination therapy (RR = 1·17, 95% CI [1·06, 1·29]) compared to nivolumab, with low heterogeneity [$p = 0{\cdot}17$, $I^2 = 44\%$] (Figure 10). One of the clinical trials found a frequency of AEs among the combination group vs. ipilimumab alone of 90% vs. 100%.

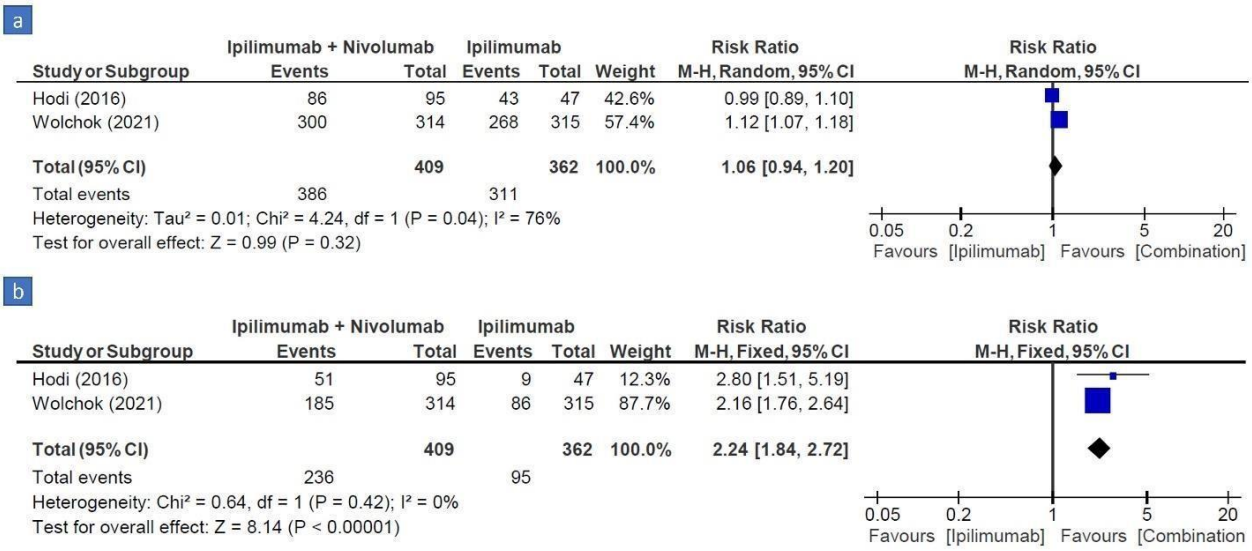

Figure 9: Forest plots of adverse events between combination therapy and Ipilimumab. (a) AE of any grade. (b) AE grade 3-4. Own elaboration.

In regard of presenting grade 3 or higher AE, it was demonstrated that there is a higher incidence presented in combined therapy (RR = 2·24, 95% CI [1·84, 2·72]) versus ipilimumab; likewise, a higher frequency of occurrence of these events was evidenced for combination therapy (RR = 2·71, 95% CI [2·22, 3·31]) compared to nivolumab, with no heterogeneity [p = 0·42, I^2 = 0%; p 0·89, I^2 = 0%, respectively]. In one of the clinical trials, a frequency of grade 3 or 4 adverse events was observed between the combination and ipilimumab-only groups of 40% vs. 56%.

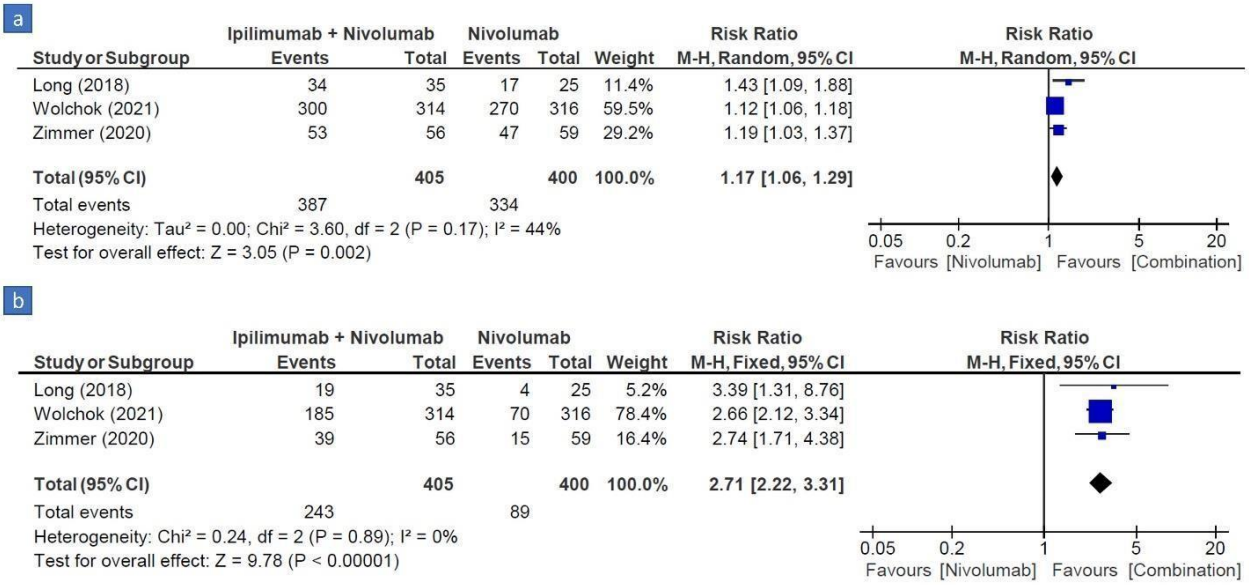

Figure 10: Forest plots of adverse events between combination therapy and nivolumab. (a) AE of any grade. (b) AE grade 3-4. Own elaboration.

Performing a meta-analysis for each adverse event reported showed that the combination of nivolumab and Ipilimumab is associated with a higher frequency of presenting AEs such as: arthralgia (RR = 1·47, 95% CI [1·09, 1·97]), increased ALT (RR = 4·23, 95% CI [3·01, 5·93]), increased AST (RR = 3·74, 95% CI [2·67, 5·25]), increased amylase (RR = 1·51, 95% CI [1·04, 2·19]), increased lipase (RR = 2·02, 95% CI [1·5, 2·72]), diarrhea (RR = 1·37, 95% CI [1·15, 1·64]), fatigue (RR = 1·41, 95% CI [1·16, 1·72]), fever (RR = 2·67, 95% CI [1·97, 3·62]), hypophysitis (RR = 1·48, 95% CI [1·08, 2·02]), hyporexia (RR = 1·57, 95% CI [1·21, 2·04]), hypothyroidism (RR = 1·56, 95% CI [1·11, 2·20]), nausea (RR = 1·88, 95% CI [1·52, 2·32]), maculopapular rash (RR = 2·00, 95% CI [1·33, 3·01]) and vomiting (RR = 2·09, 95% CI [1·51; 2·89]), with a statistically significant difference and no heterogeneity (Table 2). Another of the events observed more frequently in the combination was headache (RR = 1·35, 95% CI [0·99, 1·84]) with a statistically non-significant difference concerning monotherapy.

Adverse Event	Study	RR	95% CI		I^2 (%)
Artralgia	1,3,4,5	1,47	1,09	1,97	0
Aumento ALT	1,2,4,5	4,23	3,01	5,93	0
Aumento AST	1,2,4,5	3,74	2,67	5,25	0
Aumento amilasa	3,4,5	1,51	1,04	2,19	0
Aumento lipasa	2,3,4,5	2,02	1,50	2,72	0
Cefalea	2,3,4,5	1,35	0,99	1,84	0
Colitis	1,2,4	1,23	0,83	1,83	28
Diarrea	1,2,4,5	1,37	1,15	1,64	0
Fatiga	3,4,5	1,41	1,16	1,72	0
Fiebre	2,4,5	2,67	1,97	3,62	0
Hipofisitis	1,2,3,4,5	1,48	1,08	2,02	0
Hiporexia	2,4	1,57	1,21	2,04	0
Hipotiroidismo	2,4,5	1,56	1,11	2,20	0
Náuseas	2,4,5	1,88	1,52	2,32	0
Prurito	1,2,3,4,5	1,63	1,16	2,30	38
Rash maculopapular	1,2,4,5	2,00	1,33	3,01	0
Vitiligo	3,4	1,15	0,82	1,63	37
Vómito	2,4	2,09	1,51	2,89	0

Table 2: Meta-analysis of relative risks of adverse events of any grade between combined therapy versus monotherapy. Own elaboration.

Additional AEs that were also observed more frequently for combination therapy were pruritus (RR = 1·63, 95% CI [1·16, 2·30]), colitis (RR = 1·23, 95% CI [0·83, 1·83]), and vitiligo (RR = 1·15, 95% CI [0·82, 1·63]), all with a statistically non-significant difference, with low heterogeneity so the fixed-effect model was applied.

Sensitivity analysis

In the meta-analyses in which sensitivity analysis was performed, the results retained similarity after each study was excluded. The graphs obtained can be found in the supplement.

Publication bias

All meta-analyses have a low probability of bias according to Egger's and Begg's tests, with $p > 0{\cdot}05$. Funnel plots can be found in the supplement.

DISCUSSION

Melanoma is a cutaneous neoplasm that affects relatively young individuals, predominantly white males with fair skin, with an age of 50 years and older, whose incidence and mortality

increase with age.[1]

The programmed cell death receptor, known as PD-1, is a molecule expressed by T cells, which is used by some malignant cells to evade the immune system, so drugs targeting this receptor have been developed, such as nivolumab, approved in 2015 by the FDA, which is an antibody that blocks the PD-1 receptor thus promoting T cell- mediated anti-tumoral activity, with particular use for the treatment of several types of cancer such as melanoma, non-small cell lung cancer, and renal cancer.[23,24]

Another molecule that is usually expressed on the surface of T cells is the cytotoxic T-lymphocyte-asociated antigen-4, also known as CTL-4, which, as with the PD-1 receptor, is used by tumor cells to inactivate the T cell and avoid the immune response. Among the drugs targeting this receptor is ipilimumab, which has also been approved by the FDA and has been shown to increase overall survival in patients with stage IV melanoma, especially when combined with nivolumab, achieving greater antitumor efficacy.[3,24]

There have been studies similar to this one evaluating the efficacy and safety of nivolumab and ipilimumab combination therapy. Zhu et al. compared Ipilimumab found for the combination of a higher PR (RR = 2·82, 95% CI [2·09, 3·81]), HR (RR = 4·48, 95% CI [2·73, 7·33]) and ORR (RR = 3·31, 95% CI [2·60, 4·20]), in addition to longer OS (HR = 0·55, 95% CI [0.45; 0.67]) and similarity in the presentation of AE (RR = 1.00, 95% CI [0·97, 1·02]), with a higher incidence in cases of grade 3 or higher AE for the combination therapy group (RR = 1·81, 95% CI [1·15, 2·86]),[25] findings compatible with those found in our review. Another study that also compared combination therapy versus ipilimumab was that of Menshawy et al., who found in favor of combination therapy a higher PR (RR = 2·80, 95% CI [2·16, 3·64]), HR (RR = 5·93, 95% CI [2·45, 14·37]), and ORR (RR = 3·58, 95% CI [2·08, 6·14]), in addition to a longer PFS time (HR = 0·67, 95% CI [0·60, 0·74]), findings that were also similar to those obtained in our review,[16] findings similar to those obtained in our study.

The efficacy and safety of the combination of nivolumab and ipilimumab versus nivolumab have also been compared. Similar to our investigation, a higher ORR (RR = 1·40, 95% CI [1·27, 1·54]), longer PFS time (HR = 0·83, 95% CI [0·77, 0·90]), and higher risk of occurrence of SA (RR = 1·76, 95% CI [1·46, 2·12]) were observed for the combination, however, unlike our study, there was no statistically significant difference for OS (HR = 0·93, 95% CI [0·84, 1·03]).[20] Another study also found superiority of the combination versus nivolumab alone in terms of PFS (HR = 0·81, 95% CI [0·72, 0·91]) and OS with no clear statistically significant difference (HR = 0·87, 95% CI [0·76, 1·00]).[14]

The results of our study coincide with most of the findings provided by different studies of similar characteristics. In our case, we obtained a higher PR and ORR for combination therapy than Ipilimumab; however, there was no statistically significant difference for these same outcomes when comparing combination therapy with nivolumab. Similarly, we found a longer PFS and OS for combination therapy versus Ipilimumab, although in this case, there was also no statistically significant difference when comparing combination therapy with nivolumab.

Regarding adverse events, we found a higher risk of presenting any adverse event in the combination therapy group versus nivolumab; however, there was no statistically significant difference between combination therapy and ipilimumab, in contrast to the risk of presenting grade 3 or 4 AEs that were higher for combination therapy compared to nivolumab or Ipilimumab in monotherapy.

Finally, we observed that all the AEs studied had a higher risk of occurrence among those who received combined therapy than monotherapy, except for headache, colitis, and vitiligo, in which no statistically significant difference was observed.

The AEs with the highest association were increased ALT, AST, fever, vomiting, and increased lipase, suggesting that in these cases greater attention should be paid to the hepatopancreatic function.

It is essential to state that one of the clinical trials presented contradictory results compared to the others; however, it was not included in the meta-analyses for the efficacy study due to the small sample involved, which could lead to an erroneous estimation of the results obtained in our study. On the other hand, it was included in the last meta-analysis of adverse events because it did not introduce heterogeneity compared to the other studies, as was the case with the other outcomes.

This study presents several highlights, such as the systematic and exhaustive search of articles in electronic databases and the inclusion of good quality randomized clinical trials in which there were extensive descriptions of randomization methods, follow-up of subjects, losses, and those on which double masking was applied. In addition, most of the meta-analyses were homogeneous, which implies the robustness of the information.

Among the limitations are the small number of studies that have been carried out to date on this subject and, in some cases, the small number of subjects included in the study, so the results may not be conclusive. In addition, although publication bias was low in all the meta-analyses, it should be noted that the pharmaceutical industry financed the clinical trials included in this study.

CONCLUSION

This research demonstrates that the combination therapy of ipilimumab and nivolumab has superior efficacy compared to ipilimumab monotherapy in terms of ORR, PFS, and OS for the treatment of metastatic melanoma in adults; however, there is no significant superiority of the combination compared to nivolumab monotherapy, which suggests a more significant benefit of nivolumab, either alone or in the described combination, vs. ipilimumab. On the other hand, it seems clear that there is also an increased risk of grade 3 or 4 AEs with combination therapy, primarily related to organs such as the liver and pancreas, so the toxicity of combination therapy should be monitored if this pharmacological strategy is chosen.

Since the efficacy of combination therapy is comparable to that of nivolumab alone, considering that there is a higher risk of grade 3-4 AEs with combination therapy, it seems reasonable that nivolumab monotherapy should be preferred in individuals with the characteristics of the population included in the present study.

Given that studies addressing this topic are scarce, some with small population samples, it is essential to continue conducting good quality clinical trials that will allow a better understanding of the benefits and risks of the therapies included in this review in the future.

Contributors

All authors contributed to developing the manuscript. All authors have read and approved

the final version of the paper for submission.

Authors' contributions

Jonathan Sierra: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, writing-original draft, writing-review & editing

Alexandra Porras: Data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing-review & editing

Alejandro Rico: Data curation, investigation, methodology, resources, writing-review & editing

Declaration of interests

The authors declare that they have no competing interests.

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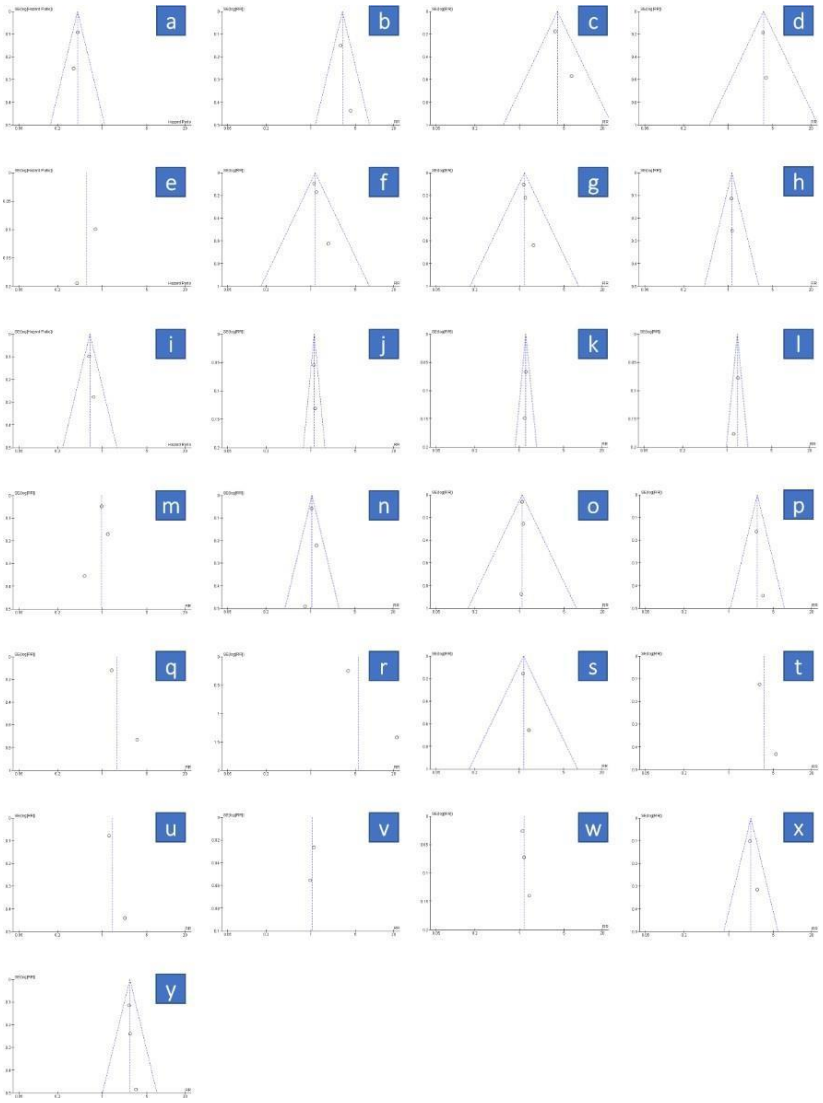
ANNEX



Funnel plots of combination [C] vs Ipilimumab (I) or nivolumab (N): (a) HR of PFS [C vs I]. (b) PFS at 12 months [C vs. I]. (c) PFS at 18 months [C vs I]. (d) PFS at 24 months [C vs I]. (e) HR of PFS [C vs N]. (f) PFS at 12 months [C vs. N]. (g) PFS at 18 months [C vs. N]. (h) PFS at 24 months [C vs N]. (i) HR of OS [C vs I]. (j) OS at 12 months [C vs. I]. (k) OS at 18 months [C vs I]. (l) OS at 24 months [C vs. I]. (m) OS at 12 months [C vs. N]. (n) OS at 18 months [C vs N]. (o) OS at 24 months [C vs N]. (p) PR [C vs I]. (q) PR [C vs N]. (r) CR [C vs. I]. (s) CR [C vs. N]. (t) ORR [C vs. I]. (u) ORR [C vs N]. (v) AE of any grade [C vs. I]. (w) AE of any grade [C vs N]. (x) AE grade 3-4 [C vs I]. (y) AE grade 3-4 [C vs N]. Own elaboration.