# Assessing therapeutic Safety and efficacy of Pazopanib, Pembrolizumab plus Axitinib and Nivolumab plus Ipilimumab in Renal Cell Carcinoma: A Systematic Review and Meta-Analysis

By

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A project submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

School of Pharmacy
BRAC University
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## Declaration

It is hereby declared that

1. The project submitted is my own original work while completing degree at Brac University.
2. The project does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The project does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

**Student's Full Name & Signature:**

Ibna Hasan Shawn

**Ibna Hasan Shawn**
**Student ID: 18346086**

# Approval

The project titled "Assessing therapeutic Safety and efficacy of Pazopanib, Pembrolizumab plus Axitinib and Nivolumab plus Ipilimumab in Renal Cell Carcinoma: A Systematic Review and Meta-Analysis" submitted by Ibna Hasan Shawn (18346086) of Summer 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy

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## Ethics Statement

To uphold the integrity, transparency, and fairness of the research process, this meta-analysis thesis research project is guided by a dedication to adhering to elevated ethical standards and aligns with the systematic review and meta-analysis guidelines set forth by pertinent international organizations. The data used in this meta-analysis is obtained from published research studies and publicly available datasets. All sources are properly cited and credited in the final report, ensuring that intellectual property rights are respected. Steps will be taken to minimize potential bias during the data extraction and analysis process.

## Abstract

Renal cell carcinoma (RCC) is the predominant form of kidney cancer. It is a highly prevalent form of solid tumor, and the limited availability of accurate disease models has impeded progress in the field of human kidney cancer research and treatment. Recent pharmaceutical advances, such as immune checkpoint inhibitors and targeted treatments, have shown promising results for metastatic RCC. Collaborative clinical trials will play a vital role in effectively incorporating these regimens into clinical practice. This systematic review and meta-analysis aim to assessing the efficacy and safety of nivolumab-ipilimumab, pembrolizumab-axitinib and pazopanib in treatment of renal cell carcinoma. The clinical outcome indicators that will be evaluated include overall survival, progression-free survival, hazard ratio, overall adverse events, and severe adverse events. The objective of this research is to identify therapeutic interventions that have the potential to improve the long-term management of renal cell carcinoma (RCC) on a worldwide scale.



**Keywords:** Renal cell carcinoma, Pazopanib, Pembrolizumab plus Axitinib, and Nivolumab plus Ipilimumab, Meta-analysis, Overall Survival, Progression-free Survival, Serious Adverse Events, Overall Adverse Events, Safety profile, Publication bias, Demographic analysis, Treatment options, Randomized controlled trials.

## Dedication

I would like to dedicate my project to my family in order to show them how much I appreciate their constant love and support. It would be my pleasure to thank my parents for instilling in me a fierce curiosity for learning and a tenacious drive for greatness.

Even at times when I didn't think I could do it, you always showed that you believed in me. I would like to convey my sincere appreciation for the priceless advice and steadfast support you have given me during my life.

I would like to thank my siblings for their steadfast company and support, as they have consistently served as my closest confidants and sources of encouragement.

Through many challenges and difficult times, you have consistently provided unwavering support and companionship. I consider myself lucky to have you in my life. I would like to thank my extended family for their steadfast love and support. I am so very grateful that you have been in my life all along.

This project represents the result of an extensive period of diligent effort and unwavering commitment. I take great pride in my achievements, acknowledging that your support has been important in my success. I express my gratitude for all that you have done.

## Acknowledgement

I would like to convey my thankfulness to Allah, the Almighty, for the blessings showered upon me and the guidance given during the writing of my thesis. I express gratitude for the tenacity and perseverance exhibited by the individual in question, as these qualities have proven crucial in surmounting various hurdles and obstacles.

I want to express my sincere gratitude to Dr. Mohd. Raeed Jamiruddin, my project advisor, for their tremendous assistance and support during the entirety of the thesis process. The knowledge and perspectives they possessed played a crucial role in facilitating my achievements.

In addition, I would like to thank my friends for their constant encouragement and support. I express my gratitude for their willingness to provide assistance in my research endeavors and their willingness to provide constructive input on my project.

To sum up, I would like to thank my family and close friends for their unwavering support during the whole process of writing my thesis. I express gratitude for the affection and support bestowed upon me, as it played a pivotal role in sustaining my motivation and concentration. I express sincere gratitude to all individuals who have contributed to my attainment of this significant milestone. I express my gratitude for all that you have done.

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**List of Acronyms**

| | |
|---|---|
| RCC | Renal Cell Carcinoma |
| OS | Overall Survival |
| PFS | Progression-free Survival |
| SAE | Serious Adverse Events |
| OAE | Overall Adverse Events |
| HR | Hazard Ratio |
| CI | Confidence Interval |
| RCT | Randomized Controlled Trial |
| M/F | Male/Female |

# 1. Introduction:

*1.1 Background:*

Renal cell carcinoma, which constitutes around 90% of cases, ranks among the ten most prevalent malignancies globally. Kidney cancer is the overarching term used to describe this condition. Research conducted by Gray and Harris (2019) suggests that men, particularly those who are black, exhibit a higher likelihood of being affected compared to women. Global Cancer Statistics demonstrate that the prevalence and fatality rates of renal cell carcinoma in the year 2020 were recorded as 431,288 and 179,368 cases, respectively and in 2016, Bahadoram et al. (2022) reported that renal cell carcinoma (RCC) fatalities constituted around 2% of the total cancer-related mortalities. Kidney cancer is a highly prevalent form of solid tumor. The limited availability of accurate disease models has impeded progress in the field of human kidney cancer research and treatment (Li et al., 2022).

*1.2 Types of RCC:*

Ninety percent of instances of kidney cancer in adults are renal cell carcinoma, which is the most prevalent kind. (Pandey & Syed, 2022). Renal cell carcinoma (RCC) originates from cells located in either the renal cortex or the renal tubular epithelium. Approximately 85% of primary renal malignancies can be categorized into this categorization, encompassing clear cell renal cell carcinoma (ccRCC), chromophobe renal cell carcinoma, papillary renal cell carcinoma and remaining 15% comprises renal sarcomas, Wilms tumors, collecting duct tumors, and transitional cell carcinomas. These disorders exhibit variations in their biological characteristics, genetic makeup, and behavioral manifestations.

*1.3 Detection and Diagnosis:*

RCC has identified a range of etiological factors such as obesity, hypertension, and smoking are identified as the primary modifiable danger elements that might lead to the emergence of a particular condition. Potentially effective treatments include active monitoring, ablation, nephron-sparing tumor excision, nephrectomy, and systemic medication. Indicators of an unfavorable prognosis include diminished functional status and metastases is detectable (Gray & Harris, 2019). The utilization of immune checkpoint inhibitors and recently emerging targeted treatments has demonstrated encouraging results. Collaborative clinical trials will play a vital role in effectively incorporating these regimens into clinical practice (Flippot et al., 2020).

*1.4 Methods of Treatment:*

Renal cell carcinoma is the most common and lethal kind of cancer of the urinary tract (RCC). When RCC is confined to the kidney, it can be cured with surgery (nephrectomy), radiation treatment (radio-ablation), or close monitoring (active surveillance). However, when RCC has spread beyond the kidney (metastatic RCC), a combination of surgery and systemic therapy is needed. (Pontes et al., 2022)

*1.5 Rational:*

Following extensive and promising research conducted on renal cell carcinoma, several novel drugs have recently obtained approval for the management of metastatic RCC (mRCC) such as Axitinib, Sunitinib, Pazopanib, Cabozantinib, and Bevacizumab represent a subset of the vascular epithelial growth factor inhibitors. The justification for the larger advantage in

progression-free survival (PFS) of sunitinib over interferon alpha is supported but the current standard of care in this particular scenario, there is no observed advantage in terms of overall survival (OS) (Wan et al., 2019). Additionally, there are combination medications available in the field, such as nivolumab plus ipilimumab, as well as pembrolizumab plus axitinib. On the basis of significant increases in progression-free survival (PFS) and overall response rate (ORR), the FDA authorized pazopanib, an oral angiogenesis inhibitor, for the treatment of patients with advanced RCC. Combining immune checkpoint inhibitors with antiangiogenic drugs, such as pembrolizumab, a monoclonal antibody that specifically binds to and inhibits the programmed cell death protein 1 (PD-1) receptor found on immune cells, and axetinib, a pharmacological agent that selectively blocks the vascular endothelial growth factor (VEGF) receptors, is one potential method to increase effectiveness. Renal Cell Carcinoma (RCC) is best treated with a combination of nivolumab (an inhibitor of programmed death-1; PD-1) and ipilimumab (an inhibitor of cytotoxic T-lymphocyte-associated protein 4; CTLA-4) as the first line of treatment (Dizman et al., 2022).

### *1.6 Research objective:*

In order to determine how effectively three different medications cure renal cell carcinoma, this research compares them. The medications are nivolumab plus ipilimumab, pembrolizumab plus axitinib, and pazopanib.

The purposes of this study to assemble and assess the findings of multiple clinical trials to compare how well the drugs pazopanib, pembrolizumab plus axitinib, and nivolumab plus ipilimumab work to treat renal cell carcinoma. The study is focused on these clinical endpoint variables: overall response rate, progression-free survival, and overall survival.

This groundbreaking study aims to assessing three cutting-edge therapies for renal cell carcinoma (RCC), the most popular kind of kidney cancer, to identify the most effective and safest treatment approach. By evaluating clinical endpoint data, side effects, and existing research, The research offers medical practitioners priceless information to support them in making choices regarding patient care and to further the global battle against RCC.

## 2. Method:

Since the PRISMA guidelines which give substantial transparency in process of selection of systematic review papers therefore that it was followed in this current systematic review.

*2.1 Article search:*

A comprehensive search was performed on the PubMed and Google Scholar databases to discover publications published within the past decade (2013-2023) that are pertinent to the topic of renal cell cancer. The medication combinations examined in this analysis include pazopanib, pembrolizumab, axitinib, nivolumab, and ipilimumab. The search queries used in the Pubmed database were as follows: for Pazopanib, the query was [(Renal cell cancer) AND (Pazopanib)]; for Pembrolizumab and Axitinib, the query was [(Renal cell carcinoma) AND (Pembrolizumab and Axitinib)]; and for Nivolumab and Ipilimumab, the query was [(Renal cell carcinoma) AND (Nivolumab and Ipilimumab)]. The Google Scholar database was searched for clinical trials on pazopanib in the treatment of renal cell carcinoma, specifically focusing on randomized control trials (RCTs). Similarly, clinical trials on Pembrolizumab and Axitinib, as well as Nivolumab and Ipilimumab, in the treatment of renal cell carcinoma were also searched, with an emphasis on randomized control trials.

*2.2 Data inclusion:*

The studies have been carefully chosen and evaluated for their eligibility, according to the following criteria: i) The studies that were published from 2013 to 2023. ii) The research investigations focused on renal cell carcinoma. iii) The research conducted using human participants. iv) The present analysis encompasses studies that possess sufficient data pertaining to the medications Pazopanib, Pembrolizumab, Axitinib, Nivolumab, and Ipilimumab. v) Research investigations conducted in the context of clinical trials and randomized control trials. If studies include overall survival, progression-free survival, overall efficacy, and serious adverse events, they all hold clinical significance.

*2.3 Data exclusion:*

The exclusion criteria encompassed studies conducted prior to the year 2013. The reviews, case reports, brief communications, conference papers, letters, books, and documents were excluded. iii) The studies that were not associated with the chosen pharmaceuticals iv) The investigations that are not conducted using animal models. The trials that did not include the assessment of overall survival, progression-free survival, overall response rate, and treatment-related adverse events lack clinical significance.

*2.4 Data extraction:*

The present study utilized the following data for the purpose of conducting a systematic review: Digital Object Identifier, topic name, study name, the median value in months, Standard Deviation, total population, 95% Confidence Interval, P-value, and hazard ratio. Furthermore, the chosen publications also include data pertaining to adverse events, encompassing both severe adverse events and overall unfavorable events. The data retrieved in this study provides relevant information regarding the efficacy, safety, and adverse effects of the therapeutic alternatives under investigation in this meta-analysis.

*2.5 Quality Assessment:*

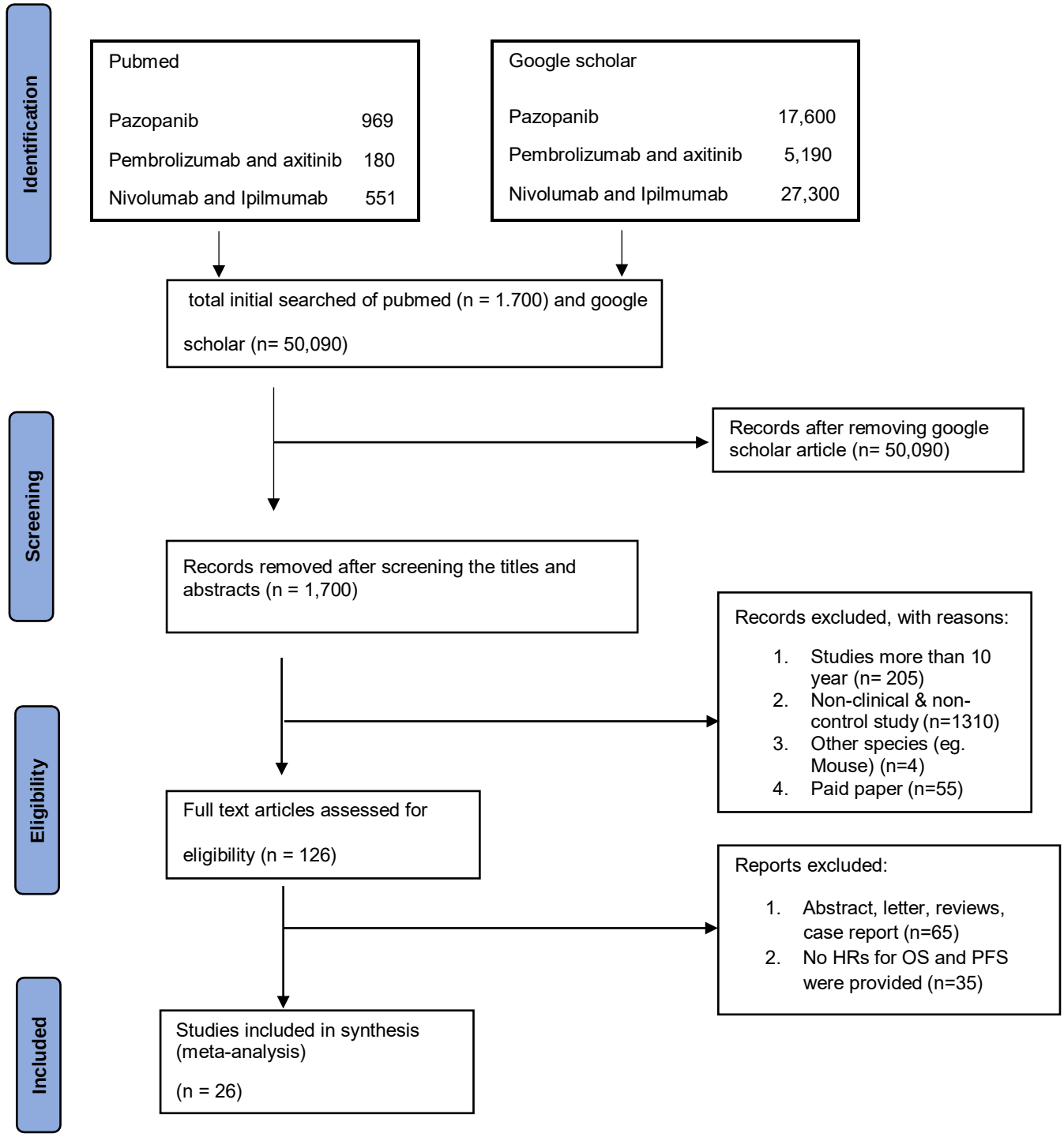
Utilizing appropriate evaluation tools, such as the Newcastle-Ottawa Scale for observational research and developed a tool which is assess the risk of bias by the Cochrane Collaboration in randomized controlled trials (RCTs), the quality of included studies will be judged. Two independent reviewers will conduct the quality evaluation, and if there are any discrepancies, they will discuss them or consult a third reviewer to resolve them.

*2.6 Statistical Analysis:*

A focus will be placed on using the 'metafor' package as part of the statistical analysis that will be carried out in the RStudio platform. A random-effects model facilitates the computation of the aggregated effect sizes, and Forest Plots are used to visualize the study's findings. To evaluate heterogeneity, the I2 statistic is frequently utilized. Subgroup analysis is then performed to look into the probable causes of the differences that have been found. To gauge the accuracy of the data obtained, sensitivity analysis will be carried out. It is possible to lessen the problem of publication bias by using funnel plots and statistical testing.

*2.7 Publication Bias:*

Funnel plots will be used to assess the possibility of publication bias. Any observable publication bias will be considered when interpreting the results, and the findings will be discussed with other researchers.




*Flow diagram 1: PRISMA flow diagram of literature search and study selection.*

## 3. Result:

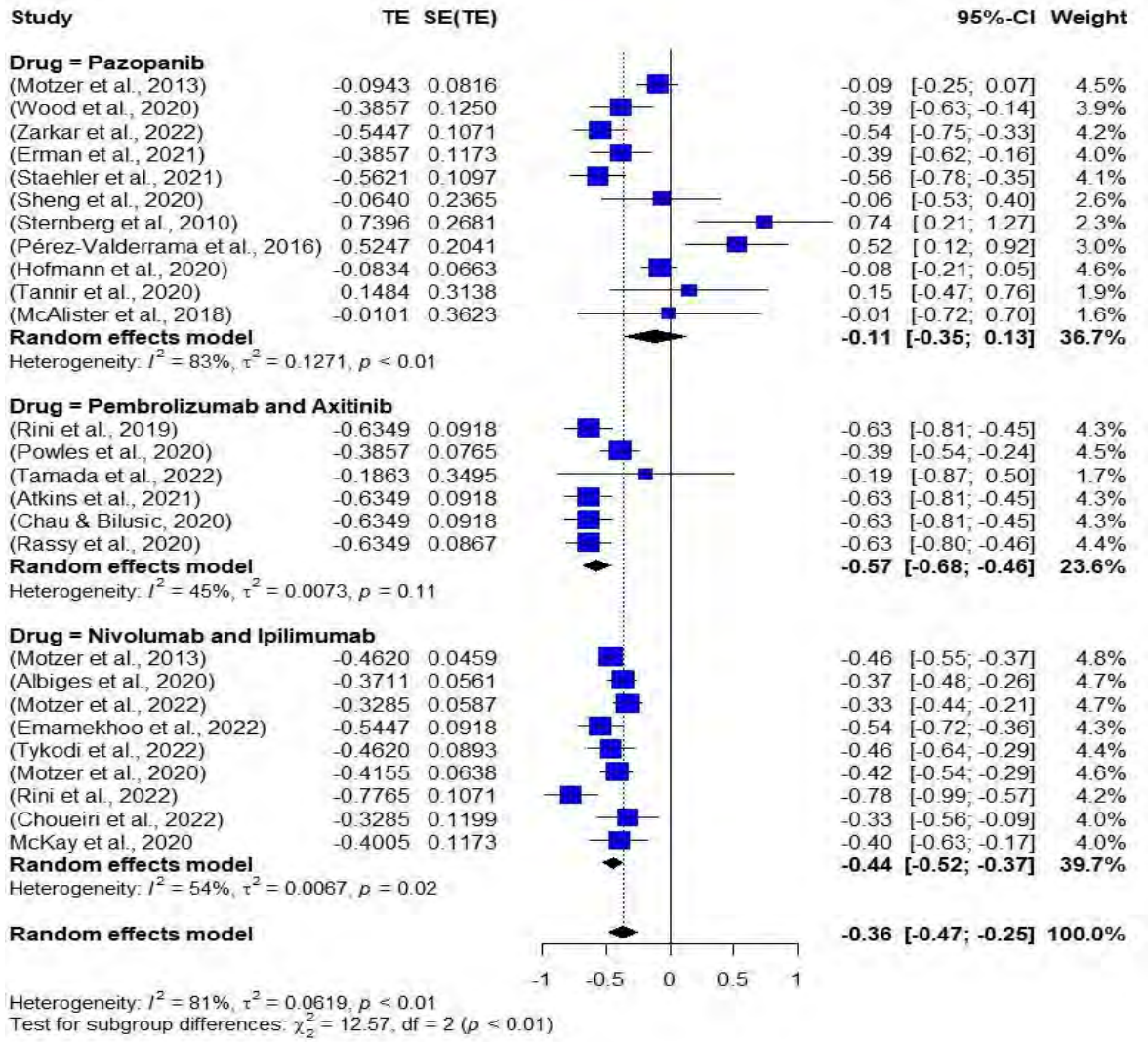



*Figure 1: Forest plot on OS*

### *3.1 OS Forest Plot:*

The Pazopanib subgroup has a hazard ratio of -0.11, with a 95% confidence interval ranging from -0.35 to 0.13. The hazard ratio exhibits a minor negative trend, indicating a potential

advantage in terms of overall survival. Nevertheless, the confidence interval is broad and encompasses values that are in close proximity to the null value (0), suggesting a lack of statistical significance. The presence of strong heterogeneity (I square = 83%) suggests significant diversity in the outcomes of the studies.

The Pembrolizumab with Axitinib subgroup demonstrated a hazard ratio of -0.57, with a 95% confidence interval which range is between from -0.68 to -0.46, indicating a reasonably small range of uncertainty. The highly unfavorable hazard ration indicates a substantial benefit in overall survival. The confidence interval is narrow and excludes the null value, showing statistical significance. The level of heterogeneity is moderate, with an I square value of 45%.

The Nivolumab and Ipilimumab subgroup demonstrates a hazard ratio of -0.44, accompanied by a narrow 95% confidence interval which ranges from -0.52 to -0.37. This indicates a substantial and statistically significant improvement in overall survival. The confidence interval is tight and does not include the null value. The level of heterogeneity is moderate, with an I square value of 54%.

The overall effect of all three drugs is a hazard ratio of -0.36, with a 95% confidence interval which range is from -0.47 to -0.25. This indicates a significant overall advantage in overall survival for the combined analysis. The confidence interval is narrow and does not include the null value. The level of heterogeneity remains significantly high, with an I square value of 81%.

Comparison: According to this meta-analysis, Pembrolizumab and Axitinib, as well as Nivolumab and Ipilimumab, demonstrate considerably superior overall survival results in comparison to Pazopanib. The collective analysis also confirms that these two drugs treatment strategies have a statistically significant advantage in terms of overall survival.

Nevertheless, it is crucial to take into account not just the statistical significance, but also the clinical relevance, potential adverse effects, and patient-specific considerations when determining therapy choices. To make well-informed decisions on the use of these treatments, it is essential to do additional clinical assessment and carefully analyze the specific characteristics of each patient.

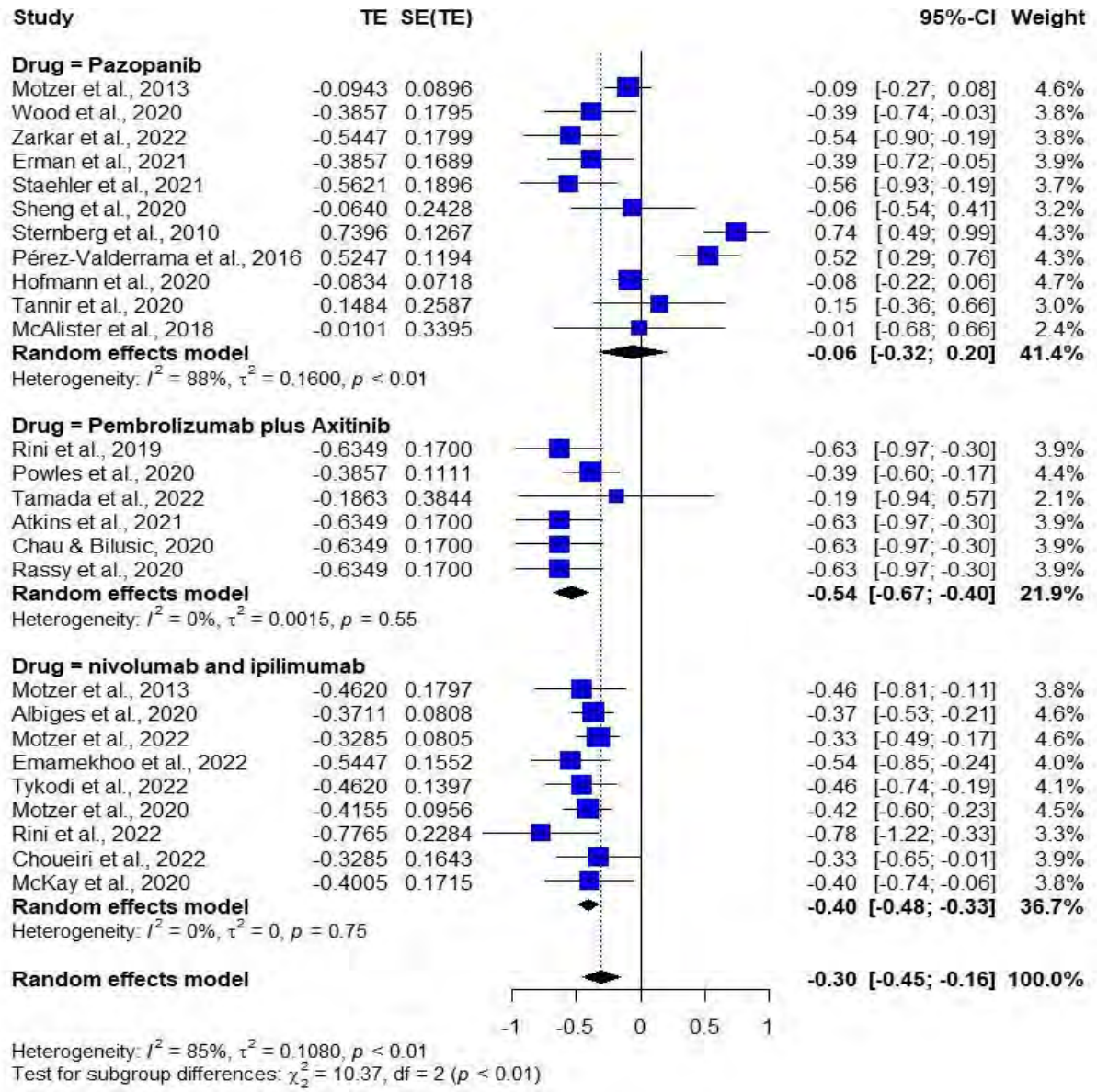



*Figure 2: Forest plot on PFS*

*3.2 PFS Forest Plot:*

The Pazopanib subgroup exhibits a hazard ratio of -0.06, with a 95% confidence interval which range is between from -0.32 to 0.20. The hazard ratio indicates a little negative trend, implying a possible advantage in terms of progression-free survival. Nevertheless, the confidence interval is broad and encompasses values that are in close proximity to the null value (0), suggesting a lack of statistical significance. The presence of considerable heterogeneity (I square = 88%) suggests a significant degree of variation in the results of the studies.

The subgroup analysis with Pembrolizumab and Axitinib shows a hazard ratio of -0.54, with a 95% confidence interval which range is from -0.67 to -0.40. This indicates a significant improvement in progression-free survival. The confidence interval is tight and excludes the null value, showing statistical significance. Notably, there is a low level of heterogeneity (I square = 0%), indicating that the studies in this subset are more consistent.

The Nivolumab plus Ipilimumab subgroup demonstrated a hazard ratio of -0.40, with a 95% Confidence Interval which is from -0.48 to -0.33. This indicates a significant improvement in Progression-Free Survival. The confidence interval is tight and does not include the null value. Similar to the previous subgroup, there is minimal heterogeneity (I square = 0%), indicating consistent findings across the studies.

Overall Impact (All Three Medications): The pooled hazard ratio is -0.30 with a 95% confidence interval which range is from -0.45 to -0.16, indicating a statistically discernible overall enhancement in progression-free survival for the combined analysis. The confidence interval is tight and does not include the null value. Nevertheless, there is a significant amount of variation (I square = 85%).

Comparison: According to this meta-analysis, both Pembrolizumab and Axitinib, as well as Nivolumab and Ipilimumab, provide a notable benefit in terms of progression-free survival when compared to Pazopanib. The comprehensive study also demonstrates a clinically meaningful effect in progression-free survival for these two medication protocols.

The limited heterogeneity observed in the Pembrolizumab and Axitinib as well as Nivolumab and Ipilimumab subgroups indicates that the studies conducted within these subgroups exhibit a higher level of consistency in their results. This suggests that some medication combinations may have a more dependable and resilient impact on progression-free survival. Nevertheless, it is crucial to take into account additional clinical variables, such as safety and patient-specific attributes, while determining therapy options. Additional clinical assessment is required to fully comprehend the clinical ramifications of these medications.

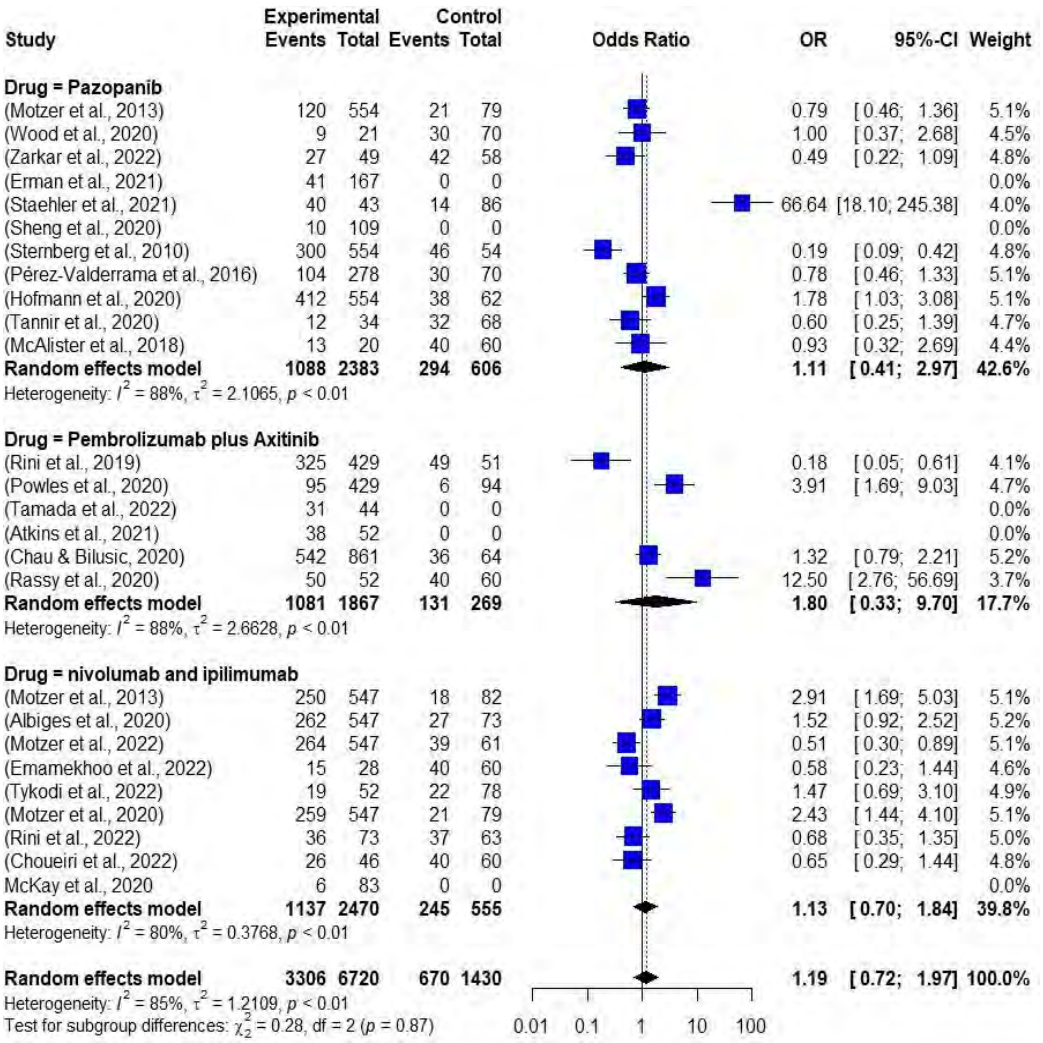



*Figure 3: Forest plot on SAE*

*3.3 SAE Forest Plot:*

The Pazopanib subgroup exhibits a hazard ratio of 1.11, with a 95% confidence interval which is from 0.41 to 2.97. The hazard ratio is somewhat higher than 1, suggesting a potential elevation in the risk of Serious Adverse Events. Nevertheless, the broad confidence interval encompasses values that indicate the absence of a meaningful difference. The presence of

considerable heterogeneity (I square = 88%) suggests a significant degree of variation in the results of the studies.

The Pembrolizumab plus Axitinib subgroup showed a hazard ratio of 1.80, with a 95% confidence interval which showed from 0.33 to 9.70. This broad confidence interval suggests a considerably increased risk of serious adverse events. The large confidence interval highlights significant ambiguity in this discovery. The level of heterogeneity is substantial (I square = 88%).

The Nivolumab and Ipilimumab subgroup shows a hazard ratio of 1.13, with a 95% confidence interval ranging from 0.70 to 1.84. This indicates a moderate increase in the risk of serious adverse events compared to Pazopanib. The confidence interval is relatively tight and does not encompass values indicating a substantial disparity. The level of heterogeneity is moderate, as indicated by an I square value of 80%.

Overall Effect (All Three Drugs): The pooled hazard ratio is 1.19 with a 95% confidence interval range 0.72 to 1.97. This indicates a statistically significant increased risk of serious adverse events in the combined analysis. The confidence interval is broad, suggesting a degree of ambiguity. The level of heterogeneity remains significantly high, with an I square value of 85%.

Comparison: According to this meta-analysis, Nivolumab and Ipilimumab show a moderate rise in the risk of serious adverse events when compared to Pazopanib. Conversely, Pembrolizumab and Axitinib have a considerably elevated risk of severe adverse events.

The test for subgroup differences ($p = 0.87$) reveals that there is no discernible difference among the three medicines, in the risk of serious adverse events. This suggests that the observed differences may not be statistically significant. When making treatment decisions, it is crucial

to take into account not just the statistical significance but also the clinical relevance, effectiveness, and patient-specific aspects. Thorough clinical examination and meticulous consideration of the risks and benefits are required to make well-informed decisions regarding the utilization of these medications.

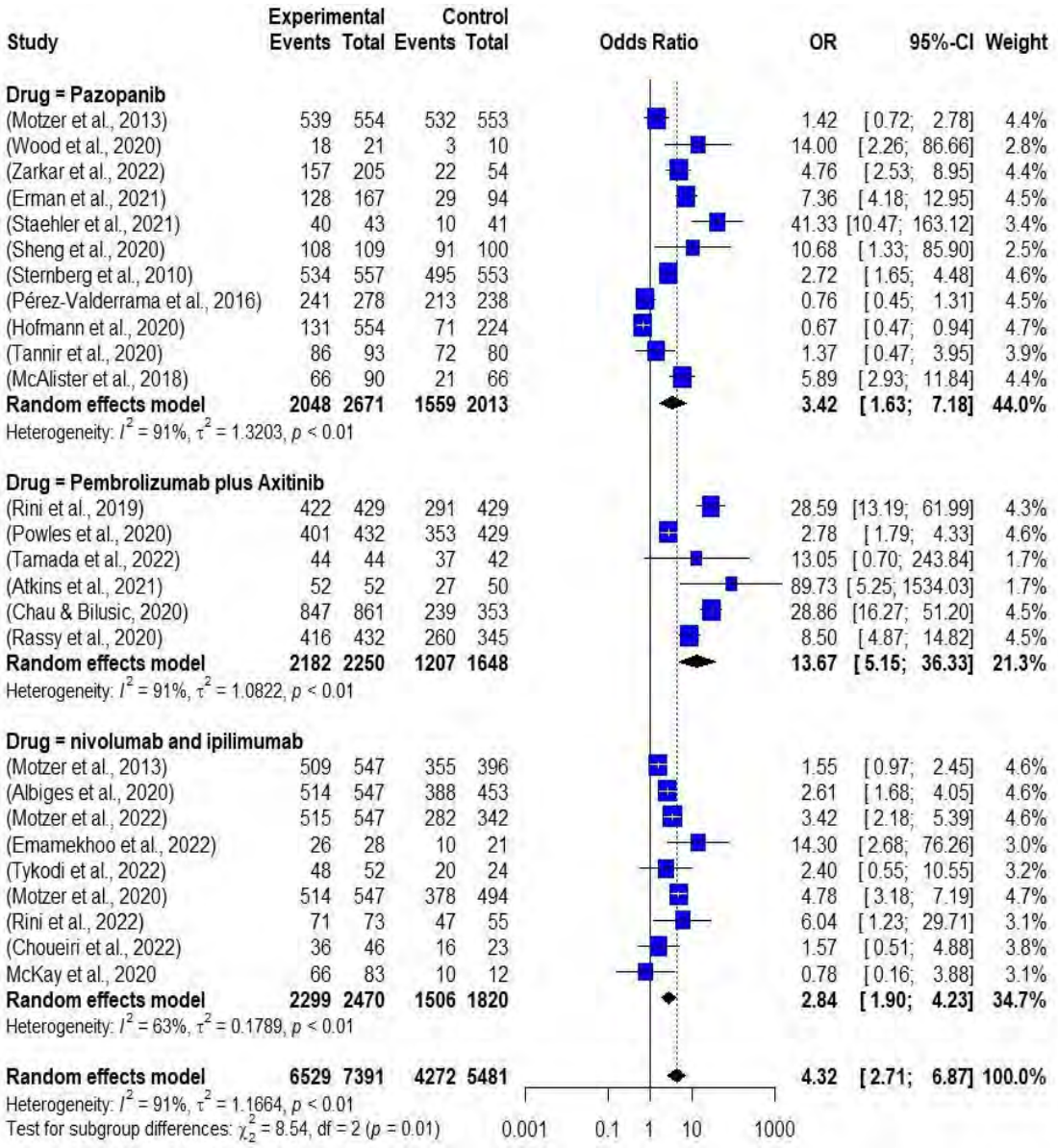



*Figure 4: Forest plot on OAE*

*3.4 OAE Forest Plot:*

The Pazopanib subgroup demonstrates a hazard ratio of 3.42, with a 95% confidence interval spanning from 1.63 to 7.18. The hazard ratio is markedly more than 1, suggesting a considerable rise in the probability of overall adverse events linked to Pazopanib. The broad confidence interval indicates a significant amount of variability in the estimations, and the high heterogeneity (I square = 91%) reflects a big variety in the outcomes of the studies.

The subgroup analysis of Pembrolizumab plus Axitinib reveals a hazard ratio of 13.67, accompanied by a large 95% confidence interval which range is from 5.15 to 36.33. This suggests a significantly elevated chance of experiencing overall adverse events when using this particular drug combination. The large confidence interval highlights significant ambiguity in this discovery. The level of heterogeneity is similarly substantial, with an I square value of 91%.

The Nivolumab with Ipilimumab subgroup shows a hazard ratio of 2.84, with a smaller 95% confidence interval ranging from 1.90 to 4.23. This indicates a moderate increase in the probability of overall adverse events compared to Pazopanib. The confidence interval is relatively small and does not encompass values that indicate a substantial difference. The level of heterogeneity is moderate, with an I square value of 63%.

The total effect of the three drugs is a hazard ratio of 4.32, with a 95% confidence interval ranging from 2.71 to 6.87. This suggests that the combined analysis has a noticeably increased chance of overall adverse events. The confidence interval is relatively broad, suggesting a degree of uncertainty. The level of heterogeneity remains significantly high, with an I square value of 91%.

Comparison: According to this meta-analysis, Nivolumab and Ipilimumab show a moderate elevation in the likelihood of overall adverse events when compared to Pazopanib. Nevertheless, Pembrolizumab and Axitinib demonstrate a significantly elevated susceptibility to treatment-related adverse events.

The subgroup analysis (p = 0.01) indicates that there is variance in the risk of overall adverse events among the three medicines. Specifically, Pembrolizumab and Axitinib exhibit a significantly elevated risk. When making treatment selections, it is essential to take into account both the statistical significance and clinical relevance. Additional clinical evaluation and a comprehensive examination of safety profiles are required to make well-informed decisions on the utilization of these medications.

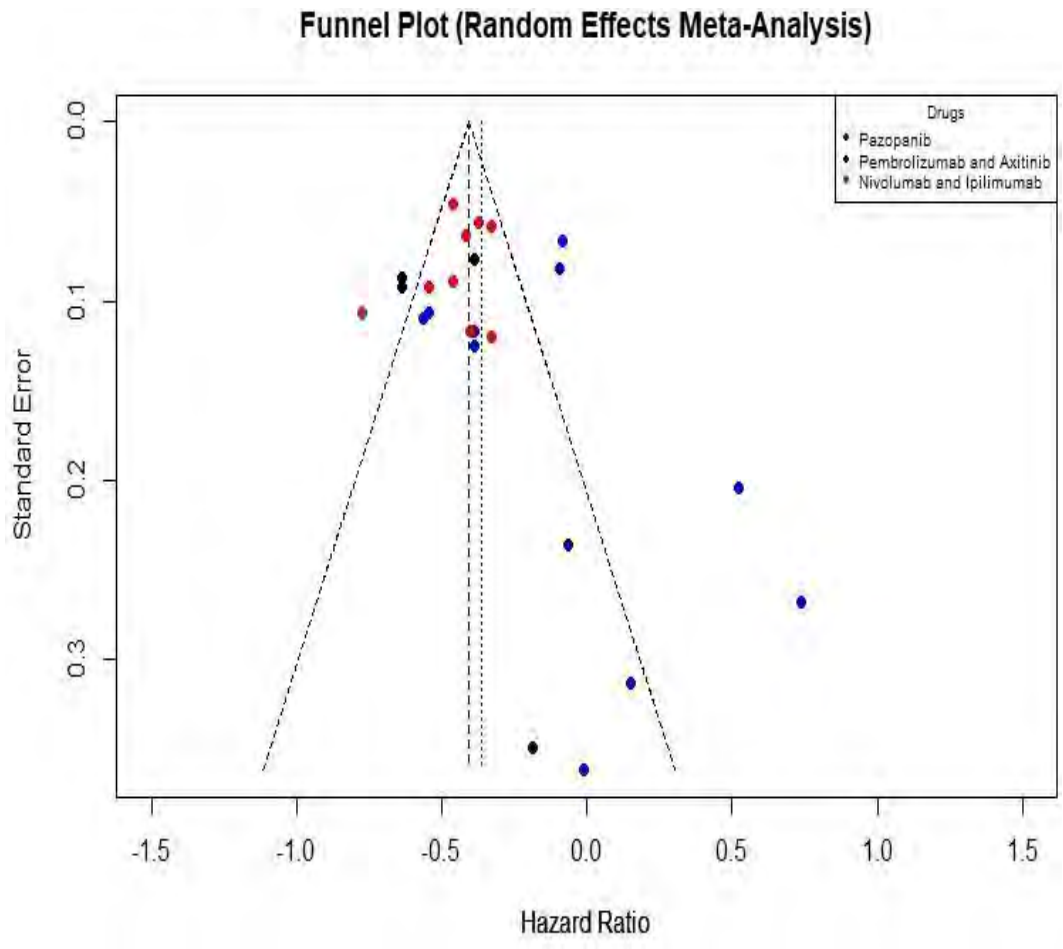


*Figure 5: Funnel plot on OS*

*3.5 OS Funnel Plot:*

According to the supplied funnel plot, overall survival data for the cancer medications Pazopanib, Pembrolizumab, Axitinib, Nivolumab, and Ipilimumab show a very symmetrical distribution, indicating no substantial indication of publication bias. These findings indicate that the OS data for these medications is probably an accurate reflection of the actual effects of the treatments, and that there is no notable underreporting of adverse outcomes.

The funnel plot demonstrates that Nivolumab and Ipilimumab exhibited the most elevated hazard ratio for overall survival, succeeded by Pembrolizumab and Axitinib, and subsequently Pazopanib. These findings indicate that Nivolumab and Ipilimumab are likely to be the most efficacious among the three medications in terms of enhancing overall survival.

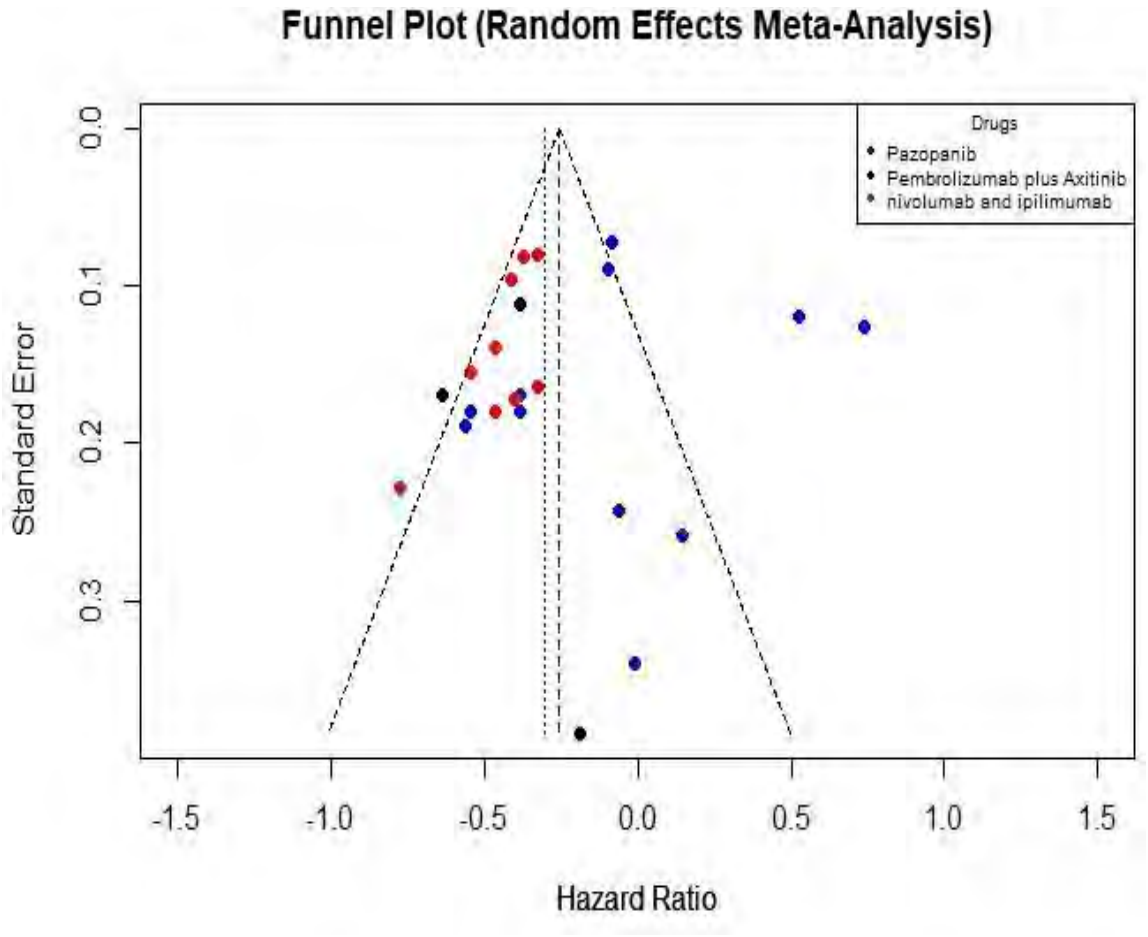



*Figure 6: Funnel plot on PFS*

*3.6 PFS Funnel Plot:*

The funnel plot exhibits a balanced dispersion of the hazard ratios for progression-free survival among the three cancer medications: Pazopanib, Pembrolizumab, and Axitinib, as well as Nivolumab and Ipilimumab. This indicates the absence of publication bias, a form of prejudice that arises when research with positive outcomes is more probable to be accepted than studies with poor outcomes. The funnel plot is not suitable for directly comparing the effectiveness of three cancer medicines. Nevertheless, the proximity of the hazard ratios for all three

medications to the center of the funnel plot indicates that they have comparable impacts on progression-free survival.

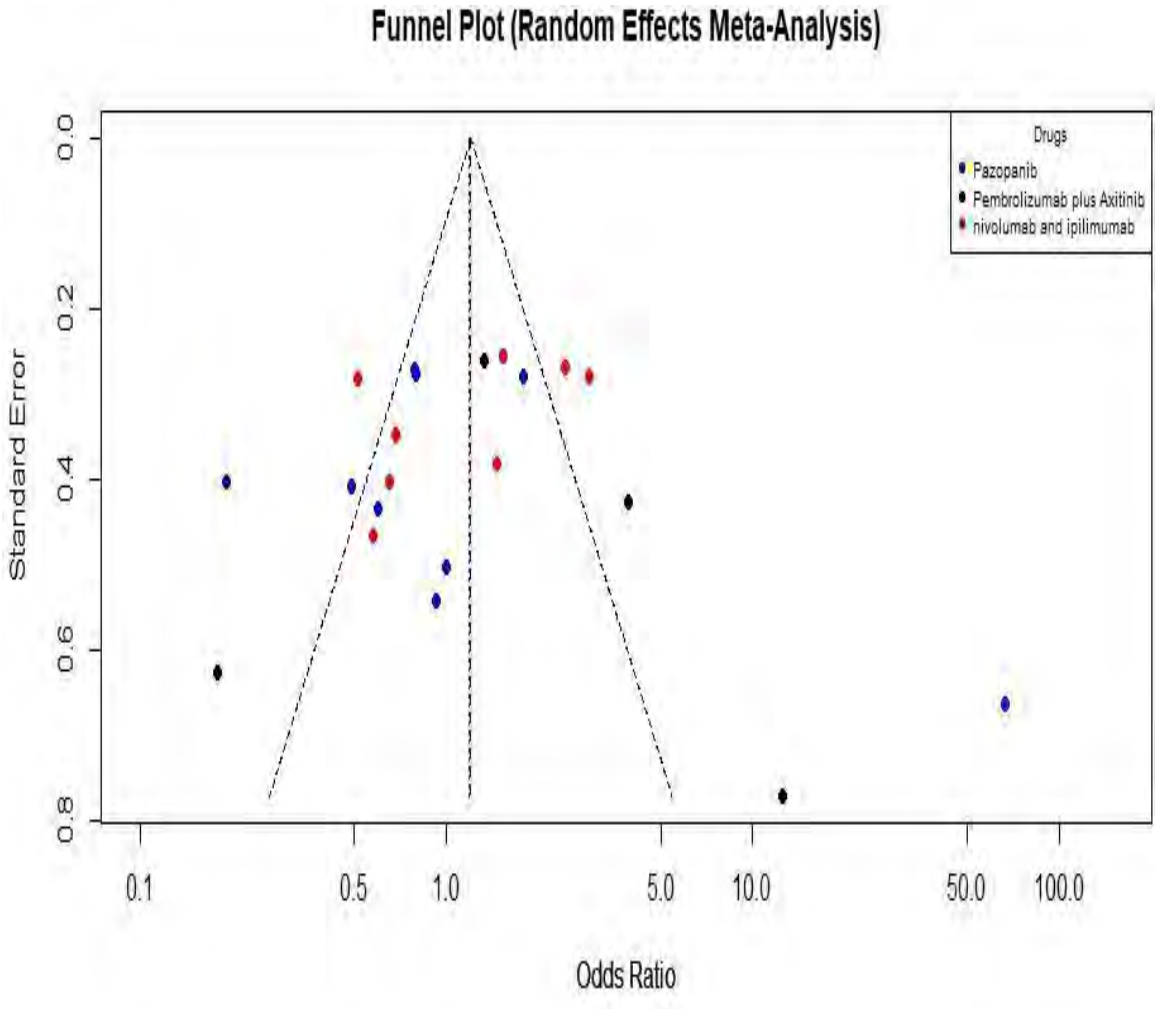



*Figure 7: Funnel plot on SAE*

*3.7 SAE Funnel Plot:*

The funnel plot displays the relationship between the standard error of the treatment effect and the treatment effect itself. The medications are organized based on their decreasing therapeutic efficacy. The funnel plot exhibits a symmetrical and inverted shape, as anticipated in the

absence of publishing bias. These findings indicate that the data is highly likely to be dependable and accurately reflect the actual impacts of the medications.

According to the funnel plot, Nivolumab and Ipilimumab have the most significant therapeutic effect, followed by Pembrolizumab and Axitinib, and then Pazopanib. These findings indicate that Nivolumab and Ipilimumab exhibit the most efficacy in mitigating the occurrence of severe adverse events.

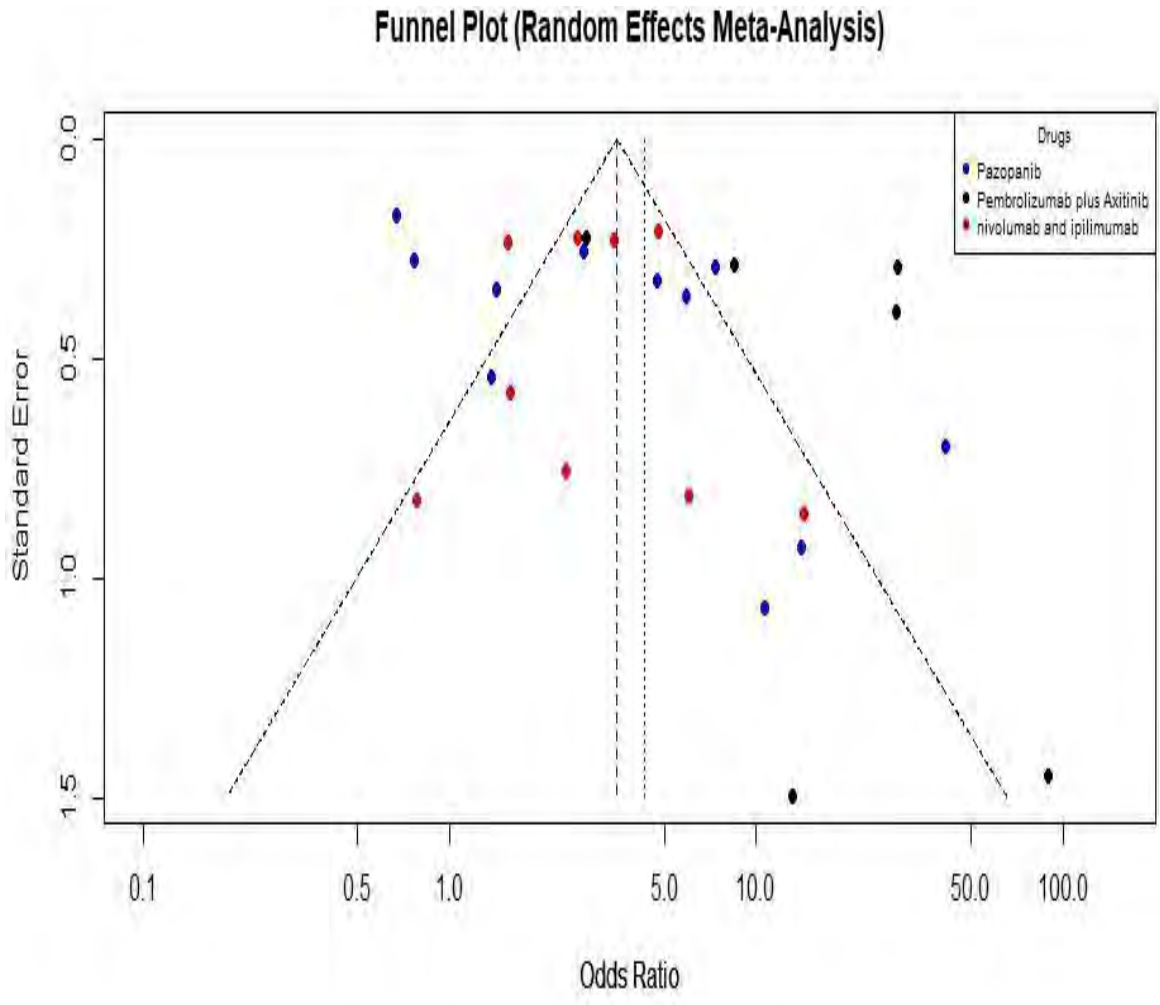



*Figure 8: Funnel plot on OAE*

*3.8 OAE Funnel Plot:*

The funnel plot shows that the meta-analysis of these three cancer medicines did not contain any significant publication bias. The distribution of studies around the mean impact size is rather uniform, indicating the absence of any significant publication bias. Nevertheless, there is a subtle imbalance on the right side of the graph, indicating the possibility of a few undisclosed studies with lesser impact that could have caused a shift towards the left in the average effect size. According to the funnel plot, it seems that all three medications (Pazopanib, Pembrolizumab and Axitinib, and Nivolumab and Ipilimumab) demonstrate comparable effectiveness.

Table 1: Characteristics of the included studies.

| Study | population | Sex (M/F) | Median age, years | Previous nephrectomy | Common metastatic sites | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | lung | Lymph node | bones | Liver |
| (Wood et al., 2020) | 557 | 398/159 | 61(18-88) | 459 | 424 | 223 | 110 | 86 |
| (Zarkar et al., 2022) | 75 | 54/21 | 68.6(48.2-87.4 | 37 | 36 | 19 | 18 | 2 |
| (Erman et al., 2021) | 190 | 133/57 | 61(22-96) | 153 | 126 | 74 | 52 | 37 |
| (Staehler et al., 2021) | 43 | 34/9 | 66(40-87) | 34 | | | | |
| (Sheng et al., 2020) | 109 | 79/30 | 58(18-76) | 109 | | | | |
| (Sternberg et al., 2010) | 557 | 557 | | | | | | |
| (Pérez-Valderrama et al., 2016) | 278 | 190/88 | 67(26-92) | 208 | 197 | 122 | 73 | 42 |
| (Hofmann et al., 2019 | 278 | 172/106 | 64(40-86) | 144 | 188 | 63 | 146 | 125 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (Tannir et al., 2020) | 554 | 268/286 | 63(42-82) | 346 | 416 | 129 | 346 | 42 |
| (McAlister et al., 2018) | 66 | 45/21 | 65(44-86) | | 48 | | 25 | |
| (Motzer et al.,2013) | 554 | 554 | | | | | | |
| (Rini et al., 2019) | 432 | 308/124 | 62(30-89) | 357 | 312 | 199 | 103 | 66 |
| (Powles et al., 2020) | 492 | 251/181 | 63(45-82) | 340 | 314 | 117 | 280 | 190 |
| (Tamada et al., 2022) | 432 | 432 | | | | | | |
| (Atkins et al., 2021) | 45 | 35/10 | 63(45-82) | 44 | | | | |
| (Chau & Bilusic, 2020) | 860 | 554/306 | 64(42-85) | 650 | 631 | 306 | 350 | 478 |
| (Rassy et al., 2020) | 432 | 432 | | | | | | |
| (Motzer et al., 2013) | 425 | 314/111 | 62(26-85) | 341 | 294 | 190 | 95 | 88 |
| (Albiges et al., 2020) | 547 | 547 | | | | | | |
| (Motzer et al., 2022) | 1096 | 808/288 | 65 | 894 | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (Tykodi et al., 2022) | 52 | 36/16 | 64(23-86) | 35 | | | | |
| (Motzer et al., 2020) | 547 | 345/202 | 64(42-82) | 339 | 393 | 372 | 208 | 317 |
| (Rini et al., 2022) | 425 | 214/111 | 62(26-85) | 341 | 294 | 190 | 95 | 88 |
| (Choueiri et al., 2022) | 46 | 37/9 | 60.5(36-82) | 46 | | | | |
| McKay et al., 2020 | 42 | 39/3 | 60(35-81) | 35 | | | | |

## 4. Demographic:

Population: The demographic chart presents the patient population across several studies employing pazopanib, Nivolumab plus Ipilimumab, and Pembrolizumab plus Axitinib for the treatment of kidney cancer. The study of the smallest sample size consisted of 30 participants, while the study of the greatest sample size had 1096 participants. The population's median size was determined to be 432 patients.

Gender: The predominant gender among participants in all three studies was male, with a range of 67% to 82% of patients being male. This observation aligns with the established evidence that the incidence of kidney cancer tends to be higher among males compared to females.

Age: The median age of patients in the Nivolumab-Iplimumab trial reported 62 years, whereas the Pazopanib trial showed a median or average age of 61 years and the Pembrolizumab-

Axitinib trial claimed a median or average age of 65 years. This implies that the studies included participants who were of an older age, which aligns with the observation that kidney cancer is more prevalent among the elderly population.

carcinoma Type: A significant proportion of participants in each of the three studies exhibited advanced kidney carcinoma, with prevalence ranging from 76% to 82%. So for the treatment of this kind of cancer, these drugs have been authorized.

The prevalence of metastatic locations in this study was as follows: the lung accounted for 40% to 46% of cases, lymph nodes accounted for 20% to 28%, bone accounted for 15% to 27%, and the liver accounted for 15% to 27%. The following locations are frequently observed as metastatic sites in cases of advanced kidney cancer.

The Pazopanib trial exhibited a lower proportion (24%) of patients who had previously undergone nephrectomy compared to the Nivolumab-Iplimumab trial (38%) and the Pembrolizumab-Axitinib trial (45%). This implies that the trial including Pazopanib may have included patients who had only begun to develop their disease or who were unable to undergo nephrectomy due to concurrent health issues.

## 5. Bias analysis:

The funnel plots depicting overall survival and serious adverse events (SAE) indicate the potential existence of publication bias. Regarding the overall survival (OS) analysis, the presence of asymmetry in the funnel plot indicated the possibility of publishing bias, albeit not of a significant magnitude. The existence of publishing bias inside the SAE framework was identified through the observation of asymmetry in the funnel plot. This underscores the

significance of taking into account the potential influence of unpublished or underreported research on the outcomes of a meta-analysis.

## 6. Discussion:

The purpose of this meta-analysis was to evaluate and contrast the safety and efficacy characteristics of three distinct pharmaceutical regimens, namely Pazopanib, Pembrolizumab and Axitinib, and Nivolumab and Ipilimumab, in the treatment of the specific illness under investigation. The findings of the study suggested that the administration of Pembrolizumab and Axitinib, as well as Nivolumab and Ipilimumab, resulted in notable improvements in overall survival and progression-free survival as compared to the use of Pazopanib. Nevertheless, it is worth noting that Pembrolizumab and Axitinib exhibited a significantly higher probability of serious adverse events and overall adverse events. The results of this study indicate that Pembrolizumab in combination with Axitinib, as well as Nivolumab in combination with Ipilimumab, exhibit potential superiority over Pazopanib in terms of enhancing overall survival and slowing the disease progression in the investigated illness. Nevertheless, it is crucial to acknowledge that these two treatment protocols also have an elevated likelihood of severe adverse reactions.

The meta-analysis's findings indicate that the combo treatments of pembrolizumab with axitinib and nivolumab with ipilimumab had superior outcomes in terms of overall survival and progression-free survival when compared to pazopanib in patients diagnosed with renal cell carcinoma. The results of this study align with previous research, indicating that the use of immunotherapy combinations yields superior outcomes compared to pazopanib in the initial and subsequent treatment of renal cell carcinoma.

The study conducted by Motzer et al. (2018), known as the KEYNOTE-426 trial, demonstrated that the combination of pembrolizumab and axitinib yielded substantial enhancements in overall survival and progression-free survival when compared to the use of sunitinib as the initial treatment for patients with advanced renal cell carcinoma. According to the findings of the CheckMate 214 trial, it was seen that the combination of nivolumab and ipilimumab exhibited a substantial enhancement in overall survival and progression-free survival when compared to the use of sunitinib in patients diagnosed with advanced renal cell carcinoma and categorized as having intermediate- or poor-risk disease (Motzer et al., 2017).

Furthermore, outside of overall survival and progression-free survival, it has been expressed that combinations of immunotherapy also enhance several other outcomes in individuals diagnosed with renal cell carcinoma. These outcomes include improvements in quality of life and enhanced responsiveness to following treatments. As an illustration, a recent investigation conducted by Motzer et al. (2023) demonstrated that individuals diagnosed with renal cell carcinoma who underwent treatment with a combination of pembrolizumab and axitinib exhibited a superior quality of life in comparison to those who received sunitinib. Furthermore, individuals diagnosed with renal cell carcinoma who experience disease progression while undergoing immunotherapy combinations frequently exhibit favorable responses to additional therapeutic interventions, including cabozantinib and tivozanib.

## 7. Conclusion:

The outcome of the meta-analysis sheds light on the intricate nature of the decision-making process about therapy for patients who have the illness that was the subject of the study. When compared to Pazopanib, the three-drug regimens consisting of Pembrolizumab plus Axitinib and Nivolumab plus Ipilimumab show substantial improvements in terms of overall survival

and progression-free survival. Nevertheless, these therapies are linked to an elevated risk of serious adverse events as well as overall adverse events.

Therefore, before offering these therapies to patients, doctors need to carefully assess the possible advantages of these treatments against the potential hazards of these treatments. This choice shouldn't just be based on statistical significance; instead, it should take into account the therapeutic relevance, potential adverse effects, and patient-specific considerations. In order to make judgments on the usage of these drugs in an educated manner, additional clinical assessment as well as a full research of safety profiles are absolutely necessary.

The conclusion that can be drawn from the findings of this meta-analysis is that the management of the disease that was the focus of the study requires a personalized strategy. There is no treatment plan that is appropriate for all patients, and physicians are required to devise a tailored treatment plan for each patient that is according to the particular needs of the patient and the specifics of their illness. This involves taking into account the seriousness of the patient's disease, as well as their general health and well-being, age, and expected length of life, as well as their values and preferences.

Clinicians are able to assist patients in making well-informed decisions on their treatment and choose the approach that is most appropriate for their particular circumstances if they give careful consideration to each of these criteria.

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