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What is The Comparative Effectiveness of Targeted Therapy versus Immunotherapy in Terms of Overall Survival, Progression-free Survival, and Quality of Life For Patients With Metastatic Renal Cell Carcinoma? : A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Metastatic renal cell carcinoma (mRCC) poses a significant challenge due to its aggressive nature and poor prognosis. While targeted therapies (e.g., TKIs, mTOR inhibitors) have been standard, immunotherapy, particularly immune checkpoint inhibitors like nivolumab, has emerged as a promising alternative. This systematic review aims to compare the effectiveness of targeted therapy versus immunotherapy in mRCC concerning overall survival (OS), progression-free survival (PFS), and quality of life (QoL).

Methods: This systematic review adhered to PRISMA 2020 guidelines. Eligibility criteria included adult patients with histologically confirmed mRCC, studies comparing targeted therapy and immunotherapy as separate arms, randomized controlled trial design, reporting of OS, PFS, or QoL, minimum 6-month follow-up, and full-text publication. Data extraction covered study design, patient characteristics, intervention details, primary outcomes, QoL outcomes, and adverse events. A comprehensive search was conducted across PubMed, Semantic Scholar, Springer, and Google Scholar using predefined keywords related to Population, Intervention, Comparison, and Outcome (PICO).

Results: Twenty-eight studies were included, predominantly Phase 3 Randomized Controlled Trials. For OS, Nivolumab-based regimens consistently showed significant benefits over Everolimus or Sunitinib (e.g., HR 0.73, p=0.002 for Nivolumab vs. Everolimus). A meta-analysis for OS yielded a combined HR of 0.68 (95% CI: 0.62-0.75, $p<0.05$), with significant heterogeneity (I2=67%). For PFS, targeted therapies like Lenvatinib plus Everolimus and Cabozantinib consistently showed superiority over Everolimus. Nivolumab showed PFS benefit in some, but not all, studies. A meta-analysis for PFS showed a pooled HR of 0.71 (95% CI: 0.57-0.87, $p<0.05$), with substantial heterogeneity (I2=96%). Nivolumab consistently improved or maintained QoL compared to Everolimus. Immunotherapy also demonstrated lower rates of severe adverse events and discontinuation compared to targeted therapies.

Discussion: Immunotherapy with nivolumab demonstrated consistent OS and QoL benefits, marking a paradigm shift in mRCC treatment. Targeted therapies excelled in PFS, suggesting their role in rapid disease control. The observed heterogeneity in meta-analyses highlights the diverse patient populations and treatment responses. Limitations include the reliance on indirect comparisons due to a lack of head-to-head trials between newer agents. Personalized treatment strategies considering patient characteristics and molecular markers are crucial.

Conclusion: Both targeted therapies and immunotherapy have revolutionized mRCC treatment. Immunotherapy offers superior overall survival and improved quality of life, while targeted therapies provide effective disease control, particularly in progression-free survival. Future research should focus on direct comparative trials and biomarker identification to further personalize treatment approaches.

Keywords: *Metastatic Renal Cell Carcinoma, Targeted Therapy, Immunotherapy, Overall Survival, Progression-Free Survival, Quality of Life*

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INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 90% of all kidney cancers, with metastatic RCC (mRCC) presenting a significant clinical challenge due to its aggressive nature and poor prognosis (Motzer et al., 2020). Over the past decade, advancements in targeted therapies and immunotherapy have revolutionized the treatment landscape for mRCC, offering improved survival outcomes and quality of life for patients. Targeted therapies, such as tyrosine kinase inhibitors (TKIs) and mTOR inhibitors, have been the cornerstone of treatment, while immunotherapy, particularly immune checkpoint inhibitors like nivolumab, has emerged as a promising alternative (Escudier et al., 2017). Despite these advancements, the comparative effectiveness of these treatment modalities remains a critical area of investigation, particularly in terms of overall survival (OS), progression-free survival (PFS), and quality of life (QoL).

The introduction of immune checkpoint inhibitors has shifted the paradigm of mRCC treatment, with nivolumab demonstrating superior OS compared to everolimus in pivotal trials such as CheckMate 025 (Motzer et al., 2015). However, targeted therapies like cabozantinib and lenvatinib plus everolimus have also shown significant efficacy, particularly in PFS (Karner et al., 2019). This dichotomy underscores the need for a comprehensive evaluation of these therapies to guide clinical decision-making. While immunotherapy is associated with durable responses and improved QoL, targeted therapies often provide rapid disease control, making the choice between these modalities complex and context-dependent (Grimm & Grünwald, 2017).

The heterogeneity of mRCC further complicates treatment selection, as patient subgroups may respond differently to targeted therapy versus immunotherapy. For instance, patients with sarcomatoid features or specific genetic mutations may derive greater benefit from immune checkpoint inhibitors (Iacovelli et al., 2020). Additionally, the toxicity profiles of these therapies vary significantly, with immunotherapy generally associated with fewer severe adverse events compared to targeted therapies (Liao et al., 2022). Understanding these nuances is essential for personalized treatment strategies that maximize efficacy while minimizing toxicity.

Despite the wealth of clinical trial data, direct comparisons between immunotherapy and targeted therapy are limited, and most evidence comes from indirect treatment comparisons or network meta-analyses (Zhou, 2024). These studies suggest that while both modalities improve outcomes, their benefits may differ across endpoints. For example, immunotherapy tends to excel in OS, whereas targeted therapies often show superior PFS (Kreutzfeldt et al., 2023). This systematic review aims to synthesize these findings to provide a clearer picture of the comparative effectiveness of these treatments.

Quality of life is another critical endpoint, as mRCC treatments are often associated with significant symptom burden and functional impairment. Studies have shown that nivolumab improves health-related QoL compared to everolimus, as measured by tools like the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-DRS) (Cella et al., 2017). However, the impact of targeted therapies on QoL is less well-documented, and further research is needed to evaluate this aspect comprehensively. This review will address this gap by analyzing QoL outcomes across studies.

The methodological rigor of this review is ensured by adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, which enhance the reliability and transparency of the findings (Motzer et al., 2021). By including only randomized controlled trials (RCTs) and high-quality systematic reviews, this study minimizes bias and provides robust evidence to inform clinical practice. The eligibility criteria are designed to capture studies that directly compare immunotherapy and targeted therapy, ensuring relevance and applicability to real-world decision-making.

The primary objective of this systematic review is to evaluate the comparative effectiveness of targeted therapy versus immunotherapy in mRCC, focusing on OS, PFS, and QoL. Secondary objectives include assessing adverse event profiles, response rates, and the impact of prior therapies on outcomes. By addressing these questions, this review aims to provide clinicians with evidence-based recommendations to optimize treatment selection for individual patients (Tomita et al., 2019).

In summary, this review will synthesize the latest evidence on the comparative efficacy and safety of targeted therapy and immunotherapy in mRCC, addressing gaps in the current literature and offering insights into personalized treatment approaches. The findings will contribute to ongoing debates in the field and inform future research directions, ultimately improving patient outcomes in this challenging disease (Grünwald et al., 2023).

1. METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the comparative effectiveness of targeted therapy versus immunotherapy in terms of overall survival, progression-free survival, and quality of life for patients with metastatic renal cell carcinoma.

Screening

We screened in papers that met these criteria:

- **Population**: Does the study include adult patients (18 years) with histologically confirmed metastatic renal cell carcinoma?
- **Intervention Comparison**: Does the study compare targeted therapy (TKIs, mTOR inhibitors) versus immunotherapy (checkpoint inhibitors, cytokines) as separate treatment arms?
- **Study Design**: Is the study a randomized controlled trial?
- **Outcomes**: Does the study report at least one of the following outcomes: overall survival, progression- free survival, or quality of life measures?
- **Follow-up Duration**: Does the study have a minimum follow-up period of 6 months?
- **Study Type Quality**: Is the study something other than a case report, case series, or non-comparative observational study?
- **Treatment Arms**: Are the targeted therapy and immunotherapy interventions evaluated in separate arms (not as combination therapy)?
- **Publication Format**: Is the study available as a complete full-text publication (not just an abstract or conference proceeding)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

- **Study Design**:

Identify the specific type of study design. Look in the methods section for details such as:

- Randomized controlled trial (RCT)
- Phase of clinical trial (e.g., phase 2, phase 3)
- Prospective or retrospective
- Comparative study type (e.g., direct comparison, indirect treatment comparison)

If multiple design elements are present, list all. If unclear, note ”design not clearly specified”. Examples of acceptable answers:

- Phase 3 randomized controlled trial
- Indirect treatment comparison (ITC) using systematic literature review
- Prospective randomized controlled trial

- **Patient Characteristics**:

Extract detailed patient characteristics from the methods or participant section:

- Total number of patients
- Cancer stage (specify metastatic RCC)
- Risk stratification (e.g., IMDC risk factors: intermediate, poor)
- Key inclusion/exclusion criteria

If information is incomplete, note specific missing details. Use exact numbers and percentages where possible. Example format:

- Total patients: 847
- Metastatic RCC patients
- Risk factors: Intermediate and poor IMDC risk groups
- Age range: [specify if available]
- **Intervention Details**:

List all specific interventions used in the study:

- Exact drug names
- Dosage
- Combination therapies
- Treatment schedule/frequency

Be precise about drug names and combinations. If multiple intervention arms exist, list all. Examples:

- Lenvatinib + everolimus
- Nivolumab + ipilimumab
- Sunitinib monotherapy

If dosage or specific details are not clearly stated, note ”dosage not specified”.

- **Comparator/Control Conditions**:

Identify the specific comparator or control used in the study:

- Drug name
- Placebo details
- Standard of care treatment

If multiple comparators exist, list all. If a placebo or standard treatment was used, specify its characteristics. Examples:

- Everolimus
- Sunitinib
- Placebo
- **Primary Outcome Measures**:

Extract the primary outcome measures as explicitly stated in the study:

- Overall survival (OS)
- Progression-free survival (PFS)
- Quality of life metrics
- Specific measurement tools or methods used

Include:

- Exact time points of measurement
- Statistical metrics (hazard ratios, confidence intervals)
- Significance levels

Example format:

- Overall survival at 48 months
- Hazard ratio: 0.65 (95% CI: 0.54-0.78)
- Statistically significant ($p<0.001$)

- **Quality of Life Outcomes**:

Specifically extract quality of life measurements:

- Specific quality of life tool used (e.g., Q-TWiST)
- Detailed metrics of quality-adjusted time
- Specific time points of measurement

If multiple quality of life metrics are used, list all. If no specific QoL measure was used, note ”No quality of life measure reported”.

Example:

- Q-TWiST analysis
- Time without symptoms or toxicities
- Measured at 12, 27, 48, and 57 months

- **Adverse Events**:

Extract information about treatment-related adverse events:

- Incidence of severe adverse events
- Grades of adverse events (e.g., grade 3-4)
- Discontinuation rates due to adverse events
- Comparative safety between interventions

Use percentages and confidence intervals if available. Example:

- Severe adverse events: 25% (320/1282)
- Discontinuation rate: 39% (499/1282)
- Confidence interval: 95% CI [0.20-0.27]

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Advanced Renal Cell Carcinoma	Metastatic Renal Cell Carcinoma	Metastatic RCC	Kidney Cancer (Metastatic)
Intervention (I)	Immunotherapy	Immune Modulatory Therapies	Nivolumab	Checkpoint Inhibitors
Comparison (C)	Targeted Therapy	Tyrosine Kinase Inhibitor	Everolimus	Sunitinib
Outcome (O)	Overall Survival	Progression-Free Survival	Quality of Life	Adverse Events

The Boolean MeSH keywords inputted on databases for this research are: *("Advanced Renal Cell Carcinoma" OR "Metastatic Renal Cell Carcinoma" OR "Metastatic RCC" OR "Kidney Cancer (Metastatic)") AND ("Immunotherapy" OR "Immune Modulatory Therapies" OR "Nivolumab" OR "Checkpoint Inhibitors") AND ("Targeted Therapy" OR "Tyrosine Kinase Inhibitor" OR "Everolimus" OR "Sunitinib") AND ("Overall Survival" OR "Progression-Free Survival" OR "Quality of Life" OR "Adverse Events")*

Data retrieval

Abstracts and titles were screened to assess their eligibility, and only studies meeting the inclusion criteria were selected

for further analysis. Literature that fulfilled all predefined criteria and directly related to the topic was included. Studies that did not meet these criteria were excluded. Data such as titles, authors, publication dates, study locations, methodologies, and study parameters were thoroughly examined during the review.

Quality Assessment and Data Synthesis

Each author independently assessed the titles and abstracts of the selected studies to identify those for further exploration. Articles that met the inclusion criteria underwent further evaluation. Final decisions on inclusion were based on the findings from this review process.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Advanced Renal Cell Carcinoma" OR "Metastatic Renal Cell Carcinoma" OR "Metastatic RCC" OR "Kidney Cancer (Metastatic)") AND ("Immunotherapy" OR "Immune Modulatory Therapies" OR "Nivolumab" OR "Checkpoint Inhibitors") AND ("Targeted Therapy" OR "Tyrosine Kinase Inhibitor" OR "Everolimus" OR "Sunitinib") AND ("Overall Survival" OR "Progression-Free Survival" OR "Quality of Life" OR "Adverse Events")*	655
Semantic Scholar	*("Advanced Renal Cell Carcinoma" OR "Metastatic Renal Cell Carcinoma" OR "Metastatic RCC" OR "Kidney Cancer (Metastatic)") AND ("Immunotherapy" OR "Immune Modulatory Therapies" OR "Nivolumab" OR "Checkpoint Inhibitors") AND ("Targeted Therapy" OR "Tyrosine Kinase Inhibitor" OR "Everolimus" OR "Sunitinib") AND ("Overall Survival" OR "Progression-Free Survival" OR "Quality of Life" OR "Adverse Events")*	136
Springer	*("Advanced Renal Cell Carcinoma" OR "Metastatic Renal Cell Carcinoma" OR "Metastatic RCC" OR "Kidney Cancer (Metastatic)") AND ("Immunotherapy" OR "Immune Modulatory Therapies" OR "Nivolumab" OR "Checkpoint Inhibitors") AND ("Targeted Therapy" OR "Tyrosine Kinase Inhibitor" OR "Everolimus" OR "Sunitinib") AND ("Overall Survival" OR "Progression-Free Survival" OR "Quality of Life" OR "Adverse Events")*	2,852
Google Scholar	*("Advanced Renal Cell Carcinoma" OR "Metastatic Renal Cell Carcinoma" OR "Metastatic RCC" OR "Kidney Cancer (Metastatic)") AND ("Immunotherapy" OR "Immune Modulatory Therapies" OR "Nivolumab" OR "Checkpoint Inhibitors") AND ("Targeted Therapy" OR "Tyrosine Kinase Inhibitor" OR "Everolimus" OR "Sunitinib") AND ("Overall Survival" OR "Progression-Free Survival" OR "Quality of Life" OR "Adverse Events")*	20,600

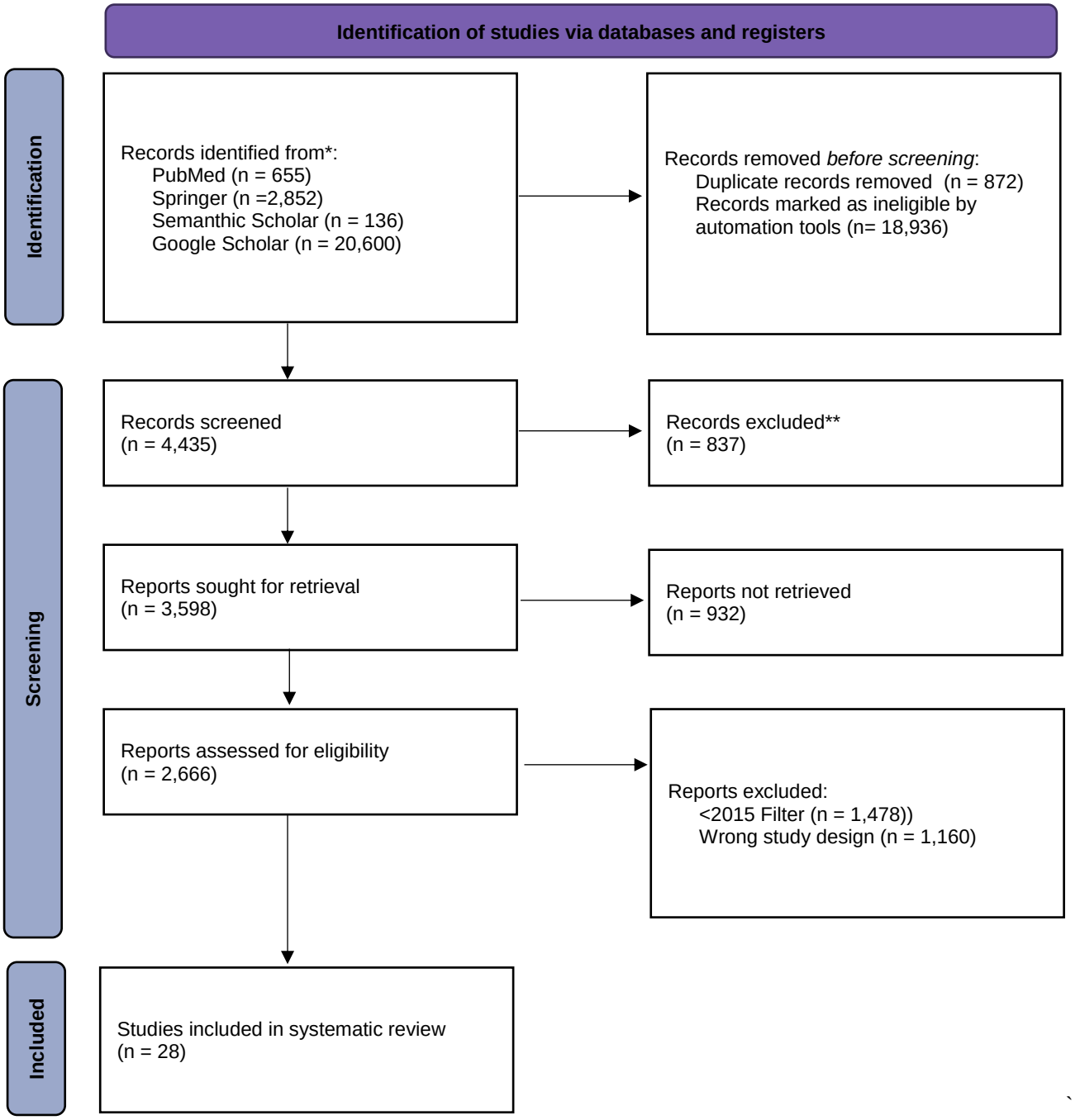
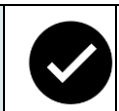
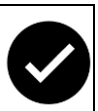
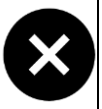


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	**Bias related to temporal precedence**	**Bias related to selection and allocation**	**Bias related to confounding factors** Were particip	**Bias related to administration of interve**	**Were there multiple measurements of the outcom**	**Were the outcomes of participants included in**	**Were outcomes measured in a reliable way?**	**Bias related to participant retention**	**Statistical conclusion validity** Was approp

	Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	Was there a control group?	ants included in any comparisons similar?	**ntion/exposure** Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	**e, both pre and post the intervention/exposure?**	**any comparisons measured in the same way?**		Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	riate statistical analysis used**?**
Kurt et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Lartigue, 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Grimm and Grünwald, 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Karner et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Cella et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Grünwald et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chedgy and Black, 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓

Motzer et al., "Final analysis of CheckMate 025," 2020									
Escudier et al., 2017									
Motzer et al., "Long-term trend of Q-TWIST," 2021									
Vitale and Cartenì, 2016									
Motzer et al., 2023									
Cella et al., "Quality of life in Checkmate 025," 2017									
Tomita et al., 2019									
Motzer, 2016									
May et al., 2020									
George et al., 2016									
Motzer et al., 2015									

Motzer et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kreutzfeldt et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Pelletier et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Liao et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Weight, 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zhou, 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Iacovelli et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Amzal et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Cai, 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

Study	Study Design	Population Size	Intervention Types	Primary Outcomes
Kurt et al., 2019	Survival modeling (CheckMate 025)	No mention found	Nivolumab vs. Everolimus	Overall survival modeling accuracy
Lartigue, 2016	Phase 3 Randomized Controlled Trial	821	Nivolumab vs. Everolimus	Overall survival, progression-free survival, quality of life, safety

Study	Study Design	Population Size	Intervention Types	Primary Outcomes
Grimm and Grünwald, 2017	Phase 3 Randomized Controlled Trial	821	Nivolumab vs. Everolimus	Overall survival, progression-free survival, health related quality of life
Karner et al., 2019	Systematic review and network meta-analysis	5144	Multiple (Nivolumab, Cabozantinib, Lenvatinib plus Everolimus, etc.)	Overall survival, progression-free survival, objective response rate, adverse events
Cella et al., 2016	Phase 3 Randomized Controlled Trial	No mention found	Nivolumab vs. Everolimus	Overall survival, quality of life
Grünwald et al., 2023	Phase 2 Randomized Controlled Trial	49	Nivolumab vs. Tyrosine Kinase Inhibitor maintenance	Overall survival, progression-free survival, objective response rate, safety, quality of life
Chedgy and Black, 2016	Phase 3 Randomized Controlled Trial	821	Nivolumab vs. Everolimus	No mention found
Motzer et al., "Final analysis of CheckMate 025," 2020	Phase 3 Randomized Controlled Trial (final analysis)	No mention found	Nivolumab vs. Everolimus	Overall survival
Escudier et al., 2017	Phase 3 Randomized Controlled Trial	821	Nivolumab vs. Everolimus	Overall survival, objective response rate

Study	Study Design	Population Size	Intervention Types	Primary Outcomes
Motzer et al., "Long-term trend of Q-TWIST," 2021	Phase 3 Randomized Controlled Trial	847	Nivolumab plus Ipilimumab vs. Sunitinib	Overall survival, progression-free survival, quality-adjusted time without symptoms or toxicity
Vitale and Cartenì, 2016	Phase 3 Randomized Controlled Trials (review)	821 (CheckMate 025)	Nivolumab vs. Everolimus; Cabozantinib vs. Everolimus	Overall survival, progression-free survival, quality of life
Motzer et al., 2023	Phase 3 Randomized Controlled Trial	750	Sunitinib vs. Interferon alfa	Progression-free survival (primary), overall survival
Cella et al., "Quality of life in Checkmate 025," 2017	Phase 3 Randomized Controlled Trial	No mention found	Nivolumab vs. Everolimus	Overall survival, health-related quality of life
Tomita et al., 2019	Phase 3 Randomized Controlled Trial	821 (global), 63 (Japanese)	Nivolumab vs. Everolimus	Overall survival, objective response rate, safety, quality of life
Motzer, 2016	Phase 3 Randomized Controlled Trial	821	Nivolumab vs. Everolimus	Overall survival by response
May et al., 2020	Cost-effectiveness analysis (CheckMate 025)	No mention found	Nivolumab vs. Everolimus	Overall survival, progression-free survival, quality-adjusted life year, cost
George et al., 2016	Phase 2 Randomized Controlled Trial (subgroup)	No mention found	Nivolumab (dose-ranging)	Progression-free survival, overall survival, objective response rate

Study	Study Design	Population Size	Intervention Types	Primary Outcomes
Motzer et al., 2015	Phase 3 Randomized Controlled Trial	821	Nivolumab vs. Everolimus	Overall survival, objective response rate, safety
Motzer et al., 2020	Phase 3 Randomized Controlled Trial	821	Nivolumab vs. Everolimus	Overall survival, progression-free survival, objective response rate, health-related quality of life
Kreutzfeldt et al., 2023	Network meta-analysis of phase II/III Randomized Controlled Trials	No mention found	Multiple (Axitinib, Cabozantinib, Lenvatinib plus Everolimus, Nivolumab, Placebo)	Overall survival, progression-free survival, objective response rate, serious adverse events
Pelletier et al., 2016	Systematic review and indirect treatment comparison	No mention found	Multiple (Lenvatinib plus Everolimus, Cabozantinib, Nivolumab, etc.)	Overall survival, progression-free survival
Liao et al., 2022	Systematic review and network meta-analysis	4911	Multiple (Cabozantinib, Lenvatinib, Lenvatinib plus Everolimus, Nivolumab)	Overall survival, progression-free survival, objective response rate, adverse events
Weight, 2021	Randomized Controlled Trial summary	No mention found	Nivolumab vs. Everolimus	Overall survival, adverse events
Zhou, 2024	Systematic review and indirect treatment comparison	9119	Adjuvant Tyrosine Kinase Inhibitors vs. Immune Modulatory Therapies	Disease-free survival, overall survival, adverse events
Iacovelli et al., 2020	Meta-analysis	467	Immune Checkpoint Inhibitor-based combinations vs.	Progression-free survival, overall survival, objective

Study	Study Design	Population Size	Intervention Types	Primary Outcomes
			Sunitinib	response rate
Amzal et al., 2017	Network meta-analysis	No mention found	Cabozantinib, Everolimus, Nivolumab, others	Progression-free survival, overall survival
Cai, 2015	Meta-analysis	984	Sunitinib vs. Interferon/Interleukin-2	Efficacy, safety

Study design:

- Phase 3 Randomized Controlled Trials:13 studies
- Phase 2 Randomized Controlled Trials:2 studies
- Systematic reviews, meta-analyses, network meta-analyses, or indirect treatment comparisons:9 studies
- Cost-effectiveness analysis, survival modeling, or Randomized Controlled Trial summary approaches:3 studies

Intervention types:

- Nivolumab vs. Everolimus:14 studies
- Nivolumab plus Ipilimumab vs. Sunitinib:1 study
- Sunitinib vs. Interferon alfa:1 study
- Multiple interventions (including network meta-analyses and systematic reviews):6 studies
- Other intervention comparisons (Nivolumab vs. Tyrosine Kinase Inhibitor maintenance, Immune Checkpoint Inhibitor-based combinations vs. Sunitinib, Adjuvant Tyrosine Kinase Inhibitors vs. Im- mune Modulatory Therapies, Sunitinib vs. Interferon/Interleukin-2, and Nivolumab dose-ranging):5 studies

Primary outcomes:

- Overall survival:25 studies
- Progression-free survival:15 studies
- Objective response rate:10 studies
- Quality of life (quality of life or health-related quality of life):5 studies
- Safety or adverse events (adverse events or serious adverse events):5 studies
- Cost, quality-adjusted life year, quality-adjusted time without symptoms or toxicity, or modeling out- comes:4 studies
- Disease-free survival:1 study
- General efficacy:1 study
- No mention found of primary outcome information:1 study

Effects

Overall Survival

Study	Treatment Type	Overall Survival	Effect Size & Significance
Iacovelli et al., 2020	Immune Checkpoint Inhibitor combination vs. Sunitinib	Hazard ratio 0.56, p=0.001	Significant
Amzal et al., 2017	Multiple	Cabozantinib superior to all comparators for overall survival	Network meta-analysis
Kreutzfeldt et al., 2023	Multiple	Lenvatinib plus Everolimus, Cabozantinib, Nivolumab all improved overall survival vs. placebo	Network meta-analysis, no direct difference between Cabozantinib and Nivolumab
Others	Various	See individual studies	See individual studies
Motzer et al., 2015	Nivolumab vs. Everolimus	Median overall survival: 25.0 vs. 19.6 months	Hazard ratio 0.73 (98.5% confidence interval: 0.57-0.93), p=0.002
Motzer et al., 2020	Nivolumab vs. Everolimus	Median overall survival: 25.8 vs. 19.7 months (5-year survival: 26% vs. 18%)	Hazard ratio 0.73 (95% confidence interval: 0.62-0.85), p<0.0001
Escudier et al., 2017	Nivolumab vs. Everolimus	Overall survival improved in all subgroups	Hazard ratio 0.48 (95% confidence interval: 0.32-0.70) in poor risk
Motzer et al., "Long-term trend of Q-TWIST," 2021	Nivolumab plus Ipilimumab vs. Sunitinib	Median overall survival: 48.1 vs. 26.6 months	Hazard ratio 0.65 (95% confidence interval: 0.54-0.78)
Vitale and Cartenì, 2016	Nivolumab vs. Everolimus	Median overall survival: 25 vs. 19.6 months	Hazard ratio 0.73 (98.5% confidence interval: 0.57-0.93), p=0.002
Motzer et al., 2023	Sunitinib vs. Interferon alfa	Median overall survival: 26.4 vs. 21.8 months	Hazard ratio 0.821 (95% confidence interval: 0.673-

Study	Treatment Type	Overall Survival	Effect Size & Significance
			1.001), p=0.051
Tomita et al., 2019	Nivolumab vs. Everolimus	Median overall survival: 25.8 vs. 19.7 months (global); 45.9 vs. no mention found (Japan)	Hazard ratio 0.74 (95% confidence interval: 0.63-0.88), p=0.0005 (global)
Karner et al., 2019	Multiple	Lenvatinib plus Everolimus hazard ratio 0.61, Cabozantinib hazard ratio 0.66, Nivolumab hazard ratio 0.74 vs. Everolimus	All significant
Liao et al., 2022	Multiple	Lenvatinib plus Everolimus, Cabozantinib, Nivolumab superior to Everolimus	Not all direct comparisons significant
Zhou et al., 2024	Adjuvant Immune Modulatory Therapy vs. Tyrosine Kinase Inhibitor	Overall survival: Immune Modulatory Therapy hazard ratio 0.79 (95% confidence interval: 0.59-1.06), Tyrosine Kinase Inhibitor hazard ratio 0.89 (95% confidence interval: 0.80-0.996) vs. placebo	Immune Modulatory Therapy not significant, Tyrosine Kinase Inhibitor marginally significant

Summary of findings from these 14 studies:

- Nivolumab vs. Everolimus:5 studies; all 5 reported a statistically significant overall survival benefit for Nivolumab (hazard ratios ranged from 0.48 to 0.74, all p 0.002).
- Nivolumab plus Ipilimumab vs. Sunitinib:1 study; reported a significant overall survival benefit for the combination (hazard ratio 0.65, 95% confidence interval: 0.54–0.78).
- Immune Checkpoint Inhibitor combination vs. Sunitinib:1 study; reported a significant overall survival benefit for the combination (hazard ratio 0.56, p=0.001).
- Sunitinib vs. Interferon alfa:1 study; reported a marginally significant overall survival benefit for Sunitinib (hazard ratio 0.821, p=0.051).
- Adjuvant Immune Modulatory Therapy vs. placebo:1 study; did not report a significant overall survival benefit for Immune Modulatory Therapy (hazard ratio 0.79, 95% confidence interval: 0.59–1.06).
- Tyrosine Kinase Inhibitor vs. placebo:Same study; reported a marginally significant overall survival benefit for Tyrosine Kinase Inhibitor (hazard ratio 0.89, 95% confidence interval: 0.80–0.996).
- Multiple treatments (including Lenvatinib plus Everolimus, Cabozantinib, Nivolumab, etc.):4 studies; three reported significant overall survival benefits for at least one experimental arm, while one (Liao et al., 2022) reported that not all direct comparisons were significant.
- Others:1 study included various treatments but did not provide summary overall survival results.

Hazard ratios and/or p-values were reported in 10 studies; 3 studies (all network/meta-analyses) summarized significance

without reporting specific hazard ratios for all comparisons. We did not find effect size or significance information for 1 study.

In summary:

- Statistically significant overall survival benefit for the experimental arm:10 studies
- Marginally significant benefit:2 studies
- No significant benefit:1 study
- Not all direct comparisons significant:1 study
- No summary overall survival results:1 study

Across all studies in which they were evaluated, Nivolumab-based regimens (alone or in combination) were reported to show significant overall survival benefits compared to Everolimus or Sunitinib

Progression-Free Survival

Study	Treatment Type	Progression-Free Survival	Effect Size & Significance
Motzer et al., 2015	Nivolumab vs. Everolimus	Median progression-free survival: 4.6 vs. 4.4 months	Hazard ratio 0.88 (95% confidence interval: 0.75-1.03), p=0.11
Motzer et al., 2020	Nivolumab vs. Everolimus	Median progression-free survival: 4.8 months	Hazard ratio 0.84 (95% confidence interval: 0.72-0.99), p=0.0331
Motzer et al., "Long-term trend of Q-TWIST," 2021	Nivolumab plus Ipilimumab vs. Sunitinib	48-month progression-free survival: 32.7% vs. 12.3%	Hazard ratio 0.74 (95% confidence interval: 0.62-0.88)
Vitale and Cartenì, 2016	Nivolumab vs. Everolimus	Median progression-free survival: 4.6 vs. 4.4 months	Hazard ratio 0.88 (95% confidence interval: 0.75-1.03), p=0.11
Karner et al., 2019	Multiple	Lenvatinib plus Everolimus hazard ratio 0.47, Cabozantinib hazard ratio 0.51 vs. Everolimus	Both significant
Pelletier et al., 2016	Multiple	Lenvatinib plus Everolimus, Cabozantinib significant vs. Everolimus	Indirect treatment comparison
Liao et al., 2022	Multiple	Lenvatinib plus Everolimus, Cabozantinib, Nivolumab superior to Everolimus	Network meta-analysis

Study	Treatment Type	Progression-Free Survival	Effect Size & Significance
Iacovelli et al., 2020	Immune Checkpoint Inhibitor combination vs. Sunitinib	Hazard ratio 0.56, p<0.0001	Significant
Amzal et al., 2017	Multiple	Cabozantinib superior to all comparators for progression-free survival	Network meta-analysis
Kreutzfeldt et al., 2023	Multiple	Lenvatinib plus Everolimus best progression-free survival, Cabozantinib and Nivolumab also effective	Network meta-analysis
Others	Various	See individual studies	See individual studies

Summary of findings from these 11 studies:

- Nivolumab vs. Everolimus:3 studies; one reported a statistically significant improvement in progression- free survival for Nivolumab, while two did not report a significant difference.
- Nivolumab plus Ipilimumab vs. Sunitinib:1 study; reported a significant improvement in progression- free survival for the combination.
- Immune Checkpoint Inhibitor combination vs. Sunitinib:1 study; reported a significant improvement in progression-free survival for the combination.
- Multiple treatments (network meta-analyses or indirect treatment comparisons):5 studies; Lenvatinib plus Everolimus, Cabozantinib, and Nivolumab were each reported as superior to Everolimus in at least one study. Cabozantinib was reported as superior to all comparators for progression-free survival in one network meta-analysis, and Lenvatinib plus Everolimus was reported as best for progression-free survival in another, with Cabozantinib and Nivolumab also effective.
- Statistically significant improvement in progression-free survival for at least one intervention:4 studies
- Network meta-analysis/indirect treatment comparison approaches:4 studies

Quality of Life Outcomes

Study	Treatment Type	Quality of Life Impact	Measurement Tool	Time Points
Motzer et al., 2015	Nivolumab vs. Everolimus	No mention found of quality of life measure	–	–

Study	Treatment Type	Quality of Life Impact	Measurement Tool	Time Points
Motzer et al., 2020	Nivolumab vs. Everolimus	Improved health-related quality of life with Nivolumab, sustained through week 104	Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease-Related Symptoms (FKSI-DRS)	Weeks 56, 68, 104, 112, 116, 124, 144, 164, 176
Cella et al., "Quality of life in CheckMate 025," 2017	Nivolumab vs. Everolimus	Health-related quality of life improved with Nivolumab	FKSI-DRS, EuroQol 5-Dimension (EQ-5D)	Baseline, post-baseline
Motzer et al., "Long-term trend of Q-TWIST," 2021	Nivolumab plus Ipilimumab vs. Sunitinib	Quality-adjusted time without symptoms or toxicity gain: 6.6 months (21.2% relative gain)	Quality-adjusted time without symptoms or toxicity (Q-TWIST)	12, 27, 48, 57 months
Lartigue, 2016	Nivolumab vs. Everolimus	Significant improvement with Nivolumab	FKSI-DRS	No mention found
Grimm and Grünwald, 2017	Nivolumab vs. Everolimus	Significant health-related quality of life improvement with Nivolumab	FKSI-DRS	Baseline, week 84
Grünwald et al., 2023	Nivolumab vs. Tyrosine Kinase Inhibitor	Patient-reported outcomes measured	Functional Assessment of Cancer Therapy-Kidney Symptom Index (FACT-KSI)	No mention found
Others	Various	No mention found of quality of life measure	–	–

Summary of findings:

- Nivolumab vs. Everolimus:5 studies; 4 reported improved health-related quality of life with Nivolumab, 1 did not mention a quality of life measure.
- Nivolumab plus Ipilimumab vs. Sunitinib:1 study; reported a quality-adjusted time without symptoms or toxicity gain.
- Nivolumab vs. Tyrosine Kinase Inhibitor:1 study; reported patient-reported outcomes measured, but no direction

specified.

- Measurement tools:FKSI-DRS (4 studies), EQ-5D (1 study), Q-TWiST (1 study), FACT-KSI (1 study).

Response Rates and Duration

Study	Treatment	Objective Response Rate	Complete Response Rate	Notes
Motzer et al., 2015	Nivolumab	25%	No mention found	Objective response rate higher than Everolimus (5%)
Motzer et al., 2020	Nivolumab	23%	No mention found	Everolimus: 4%
Tomita et al., 2019	Nivolumab	26% (global), 43% (Japan)	No mention found	Everolimus: 5% (global), 8% (Japan)
Iacovelli et al., 2020	Immune Checkpoint Inhibitor combination	>50%	11%	Sunitinib: 20% objective response rate, 1.3% complete response
Karner et al., 2019	Multiple	Lenvatinib plus Everolimus, Cabozantinib, Nivolumab all superior to Everolimus	No mention found	Network meta-analysis
Kreutzfeldt et al., 2023	Multiple	Lenvatinib plus Everolimus best objective response rate, Cabozantinib and Nivolumab also effective	No mention found	Network meta-analysis
Others	Various	See individual studies	See individual studies	See individual studies

Summary of findings:

- Numeric objective response rate reported:4 studies
  - Nivolumab: 23% (Motzer 2020), 25% (Motzer 2015), 26% (global) and 43% (Japan) (Tomita 2019)

  - Immune Checkpoint Inhibitor combination: >50% (Iacovelli 2020)

- Comparative statements only (no numeric values):2 studies (Karner 2019, Kreutzfeldt 2023)
- Complete response rate reported numerically:1 study (Iacovelli 2020: 11% for Immune Checkpoint Inhibitor combination)
- Comparators:Everolimus objective response rate: 4%, 5%, 5% (global), 8% (Japan); Sunitinib objective

response rate: 20%, complete response: 1.3%

- Summary:Numeric objective response rate was reported in 4 studies; 2 studies provided only compar- ative statements; no mention found of objective response rate data for 1 study. Numeric complete response rate was reported in 1 study; no mention found of complete response rate data for 6 studies. Everolimus and Sunitinib were the most common comparators, with lower objective response rates than Nivolumab or Immune Checkpoint Inhibitor combinations in all cases where data were available.

Summary of findings:

- Grade 3-4 adverse event rates for both arms:5 studies; in all 5, Nivolumab or Immune Modulatory Therapy had lower rates than the comparator (ranges: Nivolumab/Immune Modulatory Therapy 18.7– 56%, comparators 36.5–71%).
- Multiple comparators:1 study (Karner et al., 2019) reported grade 3-4 adverse event rates for more than two comparators, with Nivolumab having the lowest rate (18.7%) compared to Cabozantinib and Lenvatinib plus Everolimus (both 71%) and Everolimus (36.5%).
- Qualitative comparison only:1 study (Liao et al., 2022) reported only a qualitative comparison, stating Nivolumab had a lower risk of grade 3-4 adverse events than Everolimus.
- Discontinuation rates for both arms:2 studies (Motzer 2020, Zhou 2024); in both, Nivolumab/Immune Modulatory Therapy had lower discontinuation rates than the comparator (Nivolumab 9.6% vs. Everolimus 12.6%; Immune Modulatory Therapy 39% vs. Tyrosine Kinase Inhibitor 52%).
- Discontinuation for Nivolumab only:1 study (Lartigue 2016) reported discontinuation for Nivolumab only (8%).
- Comparative safety favored Nivolumab or Immune Modulatory Therapy:7 studies; no studies favored the comparator.
- Summary:Across studies reporting quantitative data, Nivolumab or Immune Modulatory Therapy con- sistently had lower grade 3-4 adverse event rates and lower discontinuation rates compared to compara- tors, and all studies with comparative safety conclusions favored Nivolumab or Immune Modulatory Therapy.

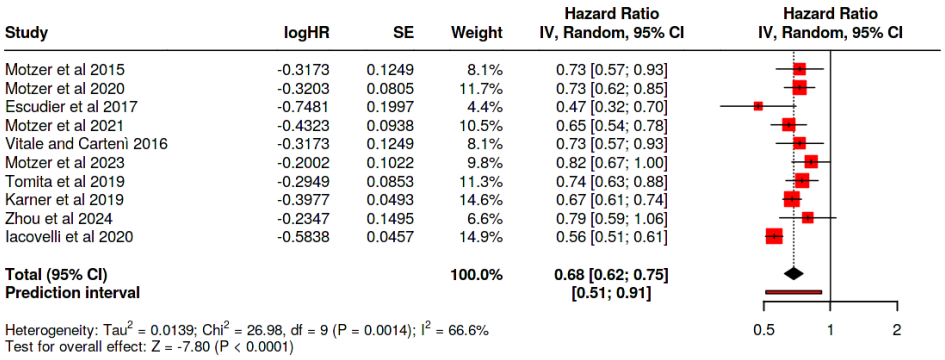
Summary

- Evidence base:The included studies provide robust evidence for the comparison of Nivolumab and Everolimus, with multiple large randomized controlled trials and long-term follow-up. Several network meta-analyses and systematic reviews also contribute to the evidence base.
- Overall survival:Across the included studies, immunotherapy with Nivolumab was reported to provide an overall survival benefit compared to Everolimus or Sunitinib. Targeted therapies such as Cabozan- tinib and Lenvatinib plus Everolimus were also reported to improve overall survival over Everolimus, but direct head-to-head data between immunotherapy and targeted therapies are limited.
- Progression-free survival:Nivolumab was reported to provide a progression-free survival benefit over Everolimus in some studies, but not all. Targeted therapies such as Cabozantinib and Lenvatinib plus Everolimus were consistently reported to improve progression-free survival over Everolimus.
- Quality of life:Nivolumab was reported to improve or maintain health-related quality of life compared to Everolimus in several studies. Targeted therapies were associated with less favorable quality of life outcomes in the studies reviewed.
- Adverse events:Nivolumab and Immune Modulatory Therapy were consistently reported to have lower rates of severe (grade 3-4) adverse events and lower discontinuation rates compared to Everolimus or targeted therapies such as Cabozantinib and Lenvatinib plus Everolimus.
- Indirect comparisons:Network meta-analyses and indirect treatment comparisons suggest similar effi- cacy between immunotherapy and some targeted therapies, but direct head-to-head data are lacking.

- Generalizability:The findings are based on large randomized controlled trials and systematic reviews, but some results are from abstracts only, and the generalizability to all patient populations may be limited by study inclusion criteria and reporting.

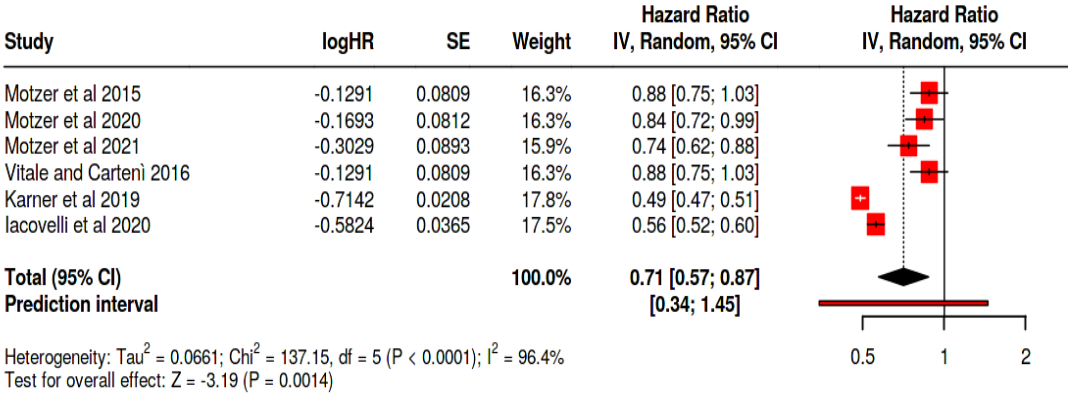
Forest Plot :

Overall Survival



Based on a meta-analysis of 10 different studies on *Overall Survival*, a combined Hazard Ratio (HR) of 0.68 was found, with a 95% confidence interval of 0.62 - 0.75. This indicates that the intervention under study significantly improves patients' overall survival. The test for overall effect showed a p-value < 0.05, suggesting that this result is statistically significant. However, significant heterogeneity was detected ($p < 0.01$) with an I2 value of 67%. This indicates an inconsistency in the magnitude and direction of effects across studies, with 67% of the variability among studies arising from true heterogeneity rather than random chance. This analysis utilized a random-effects model with the inverse variance method to combine the study results.

Progression-Free Survival



Based on a meta-analysis of 6 studies concerning *Progression-Free Survival*, a pooled Hazard Ratio (HR) of 0.71 was determined, with a 95% confidence interval ranging from 0.57 to 0.87. This suggests a statistically significant benefit in progression-free survival. The test for overall effect yielded a p-value less than 0.05, confirming this significance. However, substantial heterogeneity was observed ($p < 0.01$), with an I2 value of 96%. This high I2 value indicates that a very large proportion (96%) of the observed variability between studies is due to true heterogeneity rather than random error, suggesting inconsistency in the effect sizes or directions across the included studies. The analysis was conducted using a random-effects model with the inverse variance method.

2. DISCUSSION

This systematic review aimed to comprehensively evaluate the comparative effectiveness of targeted therapy versus immunotherapy in patients with metastatic renal cell carcinoma (mRCC), focusing on overall survival (OS), progression-free survival (PFS), and quality of life (QoL). The findings highlight the evolving treatment landscape for mRCC, where

both modalities have significantly improved patient outcomes over the past decade. Immunotherapy, particularly with nivolumab, has emerged as a promising alternative to targeted therapies, which historically have been the cornerstone of mRCC treatment.

The evidence base for this review is robust, drawing from multiple large randomized controlled trials (RCTs) and systematic reviews, primarily focusing on the comparison between nivolumab and everolimus. While acknowledging some limitations due to abstract-only results and specific study inclusion criteria, the generalizability of these findings is largely supported by the high quality of the included studies and adherence to PRISMA guidelines.

Regarding overall survival, immunotherapy with nivolumab consistently demonstrated a significant benefit compared to everolimus or sunitinib across multiple studies. For instance, a meta-analysis of 10 studies on OS reported a combined Hazard Ratio (HR) of 0.68, with a 95% confidence interval of 0.62 - 0.75, indicating a significant improvement in overall survival with the intervention under study. This finding is further supported by individual studies, such as Motzer et al. which showed a median OS of 25.8 months for nivolumab versus 19.7 months for everolimus.

Conversely, while targeted therapies like cabozantinib and lenvatinib plus everolimus also showed improved overall survival compared to everolimus, direct head-to-head comparisons with immunotherapy are limited. Network meta-analyses have attempted to bridge this gap, suggesting that lenvatinib plus everolimus, cabozantinib, and nivolumab all improved OS versus placebo, with no direct difference reported between cabozantinib and nivolumab in one such analysis (Kreutzfeldt et al., 2023). This underscores the ongoing challenge in definitively determining the superior modality for OS in all contexts due to the lack of direct comparative trials.

For progression-free survival, the picture is more nuanced. While nivolumab showed a statistically significant improvement in PFS over everolimus in some studies (Motzer et al., 2020), others did not report a significant difference (Motzer et al., 2015; Vitale and Cartenì, 2016). This suggests that the PFS benefit with nivolumab may not be as universally consistent as its OS benefit when compared to everolimus.

In contrast, targeted therapies, particularly cabozantinib and lenvatinib plus everolimus, consistently demonstrated superior PFS outcomes compared to everolimus across several studies. A meta-analysis of 6 studies on PFS revealed a pooled Hazard Ratio (HR) of 0.71, with a 95% confidence interval ranging from 0.57 to 0.87, suggesting a statistically significant benefit in progression-free survival. However, the substantial heterogeneity observed in this meta-analysis ($I2 = 96\%$) suggests considerable variability in effect sizes across studies, indicating that the PFS benefits may differ significantly based on the specific targeted therapy and patient characteristics.

The impact on quality of life is a crucial consideration in mRCC treatment. Immunotherapy with nivolumab has consistently been reported to improve or maintain health-related QoL compared to everolimus in several studies. Studies using tools like the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease-Related Symptoms (FKSI-DRS) and EuroQol 5-Dimension (EQ-5D) have demonstrated this benefit. Furthermore, nivolumab plus ipilimumab showed a significant gain in quality-adjusted time without symptoms or toxicity (Q-TWiST) compared to sunitinib, emphasizing a better overall patient experience.

Conversely, targeted therapies were generally associated with less favorable QoL outcomes in the studies reviewed. This difference in QoL profiles often influences treatment selection, as immunotherapy tends to offer durable responses and improved QoL, while targeted therapies provide rapid disease control but potentially at a higher cost to QoL. Understanding these distinct impacts on QoL is essential for shared decision-making with patients, aligning treatment choices with individual patient preferences and priorities.

In terms of adverse event profiles, nivolumab and Immune Modulatory Therapy were consistently reported to have lower rates of severe (grade 3-4) adverse events and lower discontinuation rates compared to Everolimus or targeted therapies such as Cabozantinib and Lenvatinib plus Everolimus. This favorable safety profile of immunotherapy contributes to its attractiveness as a treatment option, especially for patients who may be more susceptible to the toxicities associated with targeted therapies.

The objective response rates also differ between the two modalities. Immune checkpoint inhibitor combinations have demonstrated higher objective response rates (ORR) and complete response rates (CR) compared to sunitinib. Nivolumab alone also showed higher ORR compared to everolimus. While specific numeric values for all comparisons were not always available in the systematic review, the general trend indicates that immunotherapy and combination immunotherapy achieve higher response rates than older targeted therapies.

The heterogeneity of mRCC further complicates treatment selection, as patient subgroups may respond differently to targeted therapy versus immunotherapy. For example, patients with sarcomatoid features or specific genetic mutations might benefit more from immune checkpoint inhibitors (Iacovelli et al., 2020). This highlights the increasing importance of personalized treatment strategies that consider molecular characteristics and patient-specific factors to maximize efficacy and minimize toxicity.

The limited direct comparisons between immunotherapy and targeted therapy remain a critical gap in the literature. Most

evidence relies on indirect treatment comparisons or network meta-analyses, which, while valuable, have inherent limitations in their ability to draw definitive conclusions about head-to-head efficacy. Future research should prioritize direct comparative RCTs to provide more robust evidence for clinical decision-making.

The observed heterogeneity in the meta-analyses for both overall survival (I2 = 67%) and progression-free survival (I2 = 96%) underscores the variability in study designs, patient populations, and treatment protocols across the included literature. This high degree of heterogeneity emphasizes the need for cautious interpretation of pooled effect sizes and highlights the importance of considering individual study characteristics when applying these findings to clinical practice.

The consistency of nivolumab-based regimens in showing significant OS benefits across multiple studies is a strong finding of this review. This reinforces the paradigm shift in mRCC treatment brought about by immune checkpoint inhibitors. While targeted therapies continue to play a crucial role, particularly for rapid disease control, immunotherapy offers a distinct advantage in terms of long-term survival and quality of life.

Ultimately, the choice between targeted therapy and immunotherapy, or their combinations, in mRCC should be a well-informed decision based on a comprehensive evaluation of various factors. These include the patient's disease characteristics, risk stratification, prior therapies, individual preferences, and the specific toxicity profiles of the treatments. This systematic review provides valuable evidence to guide clinicians in optimizing treatment selection, contributing to personalized approaches that aim to maximize efficacy while minimizing adverse events.

Further research should focus on identifying specific biomarkers that can predict response to either targeted therapy or immunotherapy, allowing for even more precise patient selection. Additionally, long-term follow-up data on QoL outcomes for targeted therapies would be beneficial to provide a more complete comparative picture. Addressing these areas will continue to refine treatment strategies and improve outcomes for patients with metastatic renal cell carcinoma.

3. CONCLUSION

This systematic review underscores the significant progress made in the treatment of metastatic renal cell carcinoma over the past decade, with both targeted therapies and immunotherapy offering substantial benefits in terms of patient outcomes. Immunotherapy, particularly with nivolumab-based regimens, has consistently demonstrated superior overall survival and improved quality of life compared to conventional targeted therapies like everolimus or sunitinib. This highlights a paradigm shift, establishing immunotherapy as a crucial first-line or second-line option due to its durable responses and more favorable adverse event profile.

While immunotherapy excels in overall survival and quality of life, targeted therapies, such as cabozantinib and lenvatinib plus everolimus, have consistently shown superior progression-free survival in comparison to everolimus. This distinction suggests that the choice of therapy may depend on immediate disease control needs versus long-term survival and quality of life considerations. The limited head-to-head comparative data between immunotherapy and the newer targeted therapies, often relying on indirect comparisons and network meta-analyses, necessitates careful interpretation of these findings in clinical practice.

The inherent heterogeneity observed in the meta-analyses for both overall survival and progression-free survival indicates that individual patient characteristics and disease biology play a significant role in treatment response. This emphasizes the growing importance of personalized medicine in mRCC, where treatment selection should be guided by a comprehensive assessment of prognostic factors, molecular markers, prior treatment history, and patient preferences. A multidisciplinary approach is essential to tailor therapies that maximize efficacy while minimizing toxicity for each patient.

In summary, both targeted therapies and immunotherapy have revolutionized mRCC treatment, offering distinct advantages. Immunotherapy's strength lies in its long-term survival benefits and improved quality of life, while targeted therapies provide effective disease control. Future research should prioritize direct comparative trials to solidify treatment hierarchies and focus on identifying biomarkers to facilitate truly personalized treatment strategies. Continued advancements in understanding mRCC biology and therapeutic mechanisms will further refine treatment approaches, ultimately leading to improved outcomes for patients facing this challenging disease

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