transplantology

MDPI

Article

A Network Meta-Analysis on the Impact of Sirolimus vs. Everolimus on Malignancies After Kidney Transplantation

Sebastian Wolf [1], Stefan Schiele [2], Matthias Schrempf [1], Florian Sommer [1], Mingming Li [3], Ulrich Wirth [3], Jens Werner [3] and Joachim Andrassy [3,*]

[1] Department of General, Visceral and Transplantation-Surgery, University Hospital Augsburg, 86156 Augsburg, Germany; sebastian.michael.wolf@gmail.com (S.W.); matthias.schrempf@uk-augsburg.de (M.S.); florian.sommer@uk-augsburg.de (F.S.)
[2] Institute of Mathematics, University Augsburg, 86159 Augsburg, Germany; stefan.schiele@math.uni-augsburg.de
[3] Department of General, Visceral and Transplantation-Surgery, Ludwig-Maximilian's University, 81377 Munich, Germany; mingming.li@med.uni-muenchen.de (M.L.); ulrich.wirth@med.uni-muenchen.de (U.W.); jens.werner@med.uni-muenchen.de (J.W.)
* Correspondence: joachim.andrassy@med.uni-muenchen.de; Tel.: +49-89440076561

Abstract: Background: mTOR-Is positively influence the occurrence and course of certain tumors after solid organ transplantation. mTOR-inhibitor (mTOR-I) treatment, either alone or in combination with Calcineurininhibitors (CNIs), significantly reduces the incidence of malignancies after organ transplantation. However, there is no information on which mTOR-I, Sirolimus (SIR) or Everolimus (ERL), has a stronger anti-tumoral effect. Methods: The current literature was searched for prospective randomized controlled trials in renal transplantation. There were 1.164 trials screened, of which 20 could be included (7465 patients). We performed a network meta-analysis to analyze the relative risk of different types of mTOR-I compared to CNI treatment on malignancies after transplantation. A minimum follow-up of 24 months was mandatory for inclusion. Results: Four different types of mTOR-I treatment were analyzed in network meta-analyses—SIR mono, ERL mono, SIR with CNI, and ERL with CNI. The average follow-up of all trials was 43.8 months. All four different mTOR-I regimes showed a significant reduced relative risk for malignancies compared to a regular CNI-treatment with the strongest effect under SIR in combination with a CNI (RR 0.23, CI 0.09–0.55, $p = 0.001$). This effect remained consistent for all tumor entities except non-melanoma skin cancer (RR 0.25, CI 0.07–0.90, $p = 0.033$). Conclusions: It is well known that an mTOR-I based treatment in transplant patients reduces the risk of tumor manifestation in comparison to CNI treatment. A combination of SIR and CNI seems to be the most potent mTOR-I therapy against malignancies.

Keywords: kidney transplantation; malignancy; mTOR-inhibitor

Academic Editor: Maurizio Salvadori

Received: 29 November 2024
Revised: 7 January 2025
Accepted: 22 January 2025
Published: 24 January 2025

Citation: Wolf, S.; Schiele, S.; Schrempf, M.; Sommer, F.; Li, M.; Wirth, U.; Werner, J.; Andrassy, J. A Network Meta-Analysis on the Impact of Sirolimus vs. Everolimus on Malignancies After Kidney Transplantation. *Transplantology* **2025**, *6*, 2. https://doi.org/10.3390/transplantology6010002

1. Introduction

Kidney transplantation remains the best treatment option for patients with end-stage renal failure and shows a better outcome than long-term dialysis. The introduction of potent immunosuppressants facilitated the clinical success of organ transplantations. Nevertheless, side effects of immunosuppressant therapy and graft loss still remain a problem. According to an USRDS-based analysis, around 15.6% of kidney transplant recipients pass away within the first three years after transplantation. Of these, 76.3% have a functioning graft, which accounts for 46.8% of all graft losses [1]. Most of these patients die of cardiovascular problems, followed by infections and malignancy. In transplanted patients, tumor

diseases are the third most frequent reason for death with a functioning graft. Compared to the general population, the incidence of malignancies is about 2 to 4 times higher and shows an increase over time [2–4]. Contributing to just 3.6% of deaths with a functioning graft in the first year after transplantation, this figure rises to 16% between 2 and 5 years post-transplantation, nearing the rate of infections [5]. The progression of malignancies with concomitant immunosuppressive therapy is also more severe than without immunosuppression. For instance, the 5-year survival of patients with kidney transplant with colorectal cancer is 27%, as opposed to 75% in the normal population [6].

The most common tumors under immunosuppression are skin cancer as NMSC. Also, malignancies related to viral infections, e.g., Kaposi sarcoma, lymphomas, and cancer of the anus and vulva, have a particularly high incidence, whereas the risk of developing infection-unrelated tumors such as colon carcinoma, prostate cancer, etc., is only slightly increased [7–9]. Kidney cancer incidence is particularly increased in patients following kidney transplantation, as is liver cancer in patients with liver transplantation [10]. In addition, the type of immunosuppressant used influences the incidence of malignancies. Azathioprine and CNIs especially are confirmed to increase the incidence of certain cancers. Cyclosporin A (CsA) has even been classified as a carcinogenic drug by the International Agency for Research on Cancer [11,12].

In contrast, many studies have now demonstrated a reduction in the incidence of de novo malignancies with the use of mTOR-Is. The effect is apparent soon after transplantation, and seems to affect malignancies of different origin, but is particularly evident in the incidence and recurrence of skin tumors. This effect is also present under a combination therapy of an mTOR-I with a CNI and in other "non-skin" tumors [13].

However, it is not yet clear which mTOR-I (SIR vs. ERL) has the strongest anti-tumoral effect. As most randomized controlled trials are focused on only one of these two mTOR-Is, we collected data on the incidence of malignancies and tried to estimate the anti-tumoral effect of each mTOR-I using network metanalyses.

2. Materials and Methods

This is a network meta-analysis investigating the effects of two different mTOR-Is (SIR or ERL, monotherapy or in combination with CNI) compared to CNI treatment from randomized clinical trials (RCTs) on the incidence of post-transplant malignancies. This meta-analysis follows the reporting guidelines outlined in the Preferred Reporting Items for Meta-Analyses (PRISMA-NMA) (Supplementary Material File S1) [14].

2.1. Identification of the Eligibility Trials

The literature search was limited to prospective randomized controlled trials on kidney transplantation, excluding retrospective studies. Full-text articles were retrieved from PubMed (http://www.ncbi.nlm.nih.gov, accessed on 1 January 2021), ScienceDirect (http://www.sciencedirect.com, accessed on 1 January 2021), and the Cochrane Central Register of Controlled Trials (http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html, accessed on 1 January 2021) up to December 2020. The search utilized highly sensitive strategies for identifying eligible trials, combined with the following MeSH terms: (mTOR-inhibitor OR sirolimus OR everolimus) AND transplant AND (kidney OR renal).

2.2. Eligibility Criteria

Only prospective randomized renal transplantation trials with de novo kidney transplants were included, starting from 2004. A mandatory requirement for inclusion was that at least two treatment arms were investigated in these trials. One arm consisted of

an mTOR-I-based immunosuppression regimen (SIR or ERL), either with or without a CNI, while the second arm involved an mTOR-I-free, CNI-based immunosuppression regimen. mTOR-I introduction had to be de novo or within 6 months after transplantation. The selected trials were screened for data on post-transplant malignancy with at least a minimum follow-up of 24 months after transplantation. Information was summarized if several publications showed the same cohort of patients. Two independent reviewers conducted the screening and inclusion of articles.

2.3. Data Synthesis and Statistical Analysis

The clinical trials included in the analysis are qualitatively summarized in tables, detailing the direct and indirect comparisons.

We calculated relative risks (RRs) for the long-term incidence of malignancy (minimum 24 months) after transplantation, comparing CNI- and mTOR-I-based immunosuppression, to synthesize the available evidence. Analysis was made for all types of malignancies (NMSC included) and in a separate analysis for malignancies with NMSCs excluded. To account for potential heterogeneity, we conducted a random effects network meta-analysis to assess the relative treatment effect of the various immunosuppressants.

The method of the network analysis was performed as shown in the previous work of our research group on CMV-infections [15]. In addition to regular meta-analysis with direct comparisons of two trials (A vs. B), a network analysis can calculate indirect comparisons of several trials with one common treatment arm (A vs. C, using trials comparing A vs. B and B vs. C). Standard errors were calculated based on the incidence rates and the number of patients in each group. The meta-analysis was conducted using statistical software package R (version 4.3.1) with the netmeta package (version 4.15-1) [16]. *p*-values less than 0.05 were regarded as significant, and all confidence limits were calculated at the 95% level.

A network geometry graph was used for a visualization of the evidence in the network. To display the network, it is created in the plane. The nodes in the graph represent the various treatments, while the edges indicate the treatment comparisons that were evaluated. The thickness edges directly correlate with the number of trials and the number of patients included in the trials, which directly compare the four linked treatments.

Results of the network analysis are shown as estimates of the RRs. The results are visualized in a forest plot, arranged to reflect the treatment rankings based on the analysis.

Within-design heterogeneity was evaluated using Cochran's Q test and Higgins' I^2 statistics [17]. Based on the I^2 values, heterogeneity will be classified as not important (0% to 40%), moderate (30% to 60%), substantial (50% to 90%), or considerable (75% to 100%) [18]. Evaluation of potential statistical significance of between-design inconsistency was made using the Q statistic and corresponding tests.

2.4. Data Extraction and Methodologic Quality

Two independent reviewers collected the following data from eligible articles: total included patients, number of patients per treatment arm, type of transplanted organ, induction therapy, type and dosage of mTOR-I and CNI, timing of initiation of the mTOR-I treatment post-transplantation, trough levels, follow-up period, description and incidence of events of overall malignancies, and NMSCs long-term (minimum 24 month follow-up) post-transplantation, as well as statistical analysis on post-transplant malignancies associated with mTOR-Is and CNIs, both individually and in combination.

Three reviewers assessed the methodological quality using the Cochrane Collaboration tool and intention to treat (ITT) analysis [19,20].

3. Results

3.1. Included Trials

There were 1164 results in the initial literature search. Out of these, 20 trials were in accordance with the inclusion criteria. Thus, 7465 patients were included in total (Figure 1). The number of patients in the studies ranged from a minimum of 52 to a maximum of 2026. The average follow-up of all trials was 43.8 months (median 36 months). Of these trials, 9 RCTs used Sirolimus (SRL, Table S1, Supplementary Data) and 11 Everolimus (ERL, Table S2, Supplementary Data) as the mTOR-I. In the majority of cases, initiation of the mTOR-I was de novo or very early (within the first month; 12 trials, 60%). As an induction therapy, most of the trials employed either monoclonal or polyclonal antibodies (18 trials, 90%). Dosing of the mTOR-Is was slightly different between groups, with lower mTOR-I drug levels if used as a combination therapy with CNI. Drug levels for SIR monotherapy were 10–15 ng/mL (minimum and maximum of all trials) in the first 3 months, with a reduction afterwards to 5–10 ng/mL, in comparison to drug levels from 3 to 10 ng/mL in the SIR + CNI group. ERL monotherapy showed overall drug levels of 3–12 ng/mL, and the combination therapy 5–10 ng/mL.

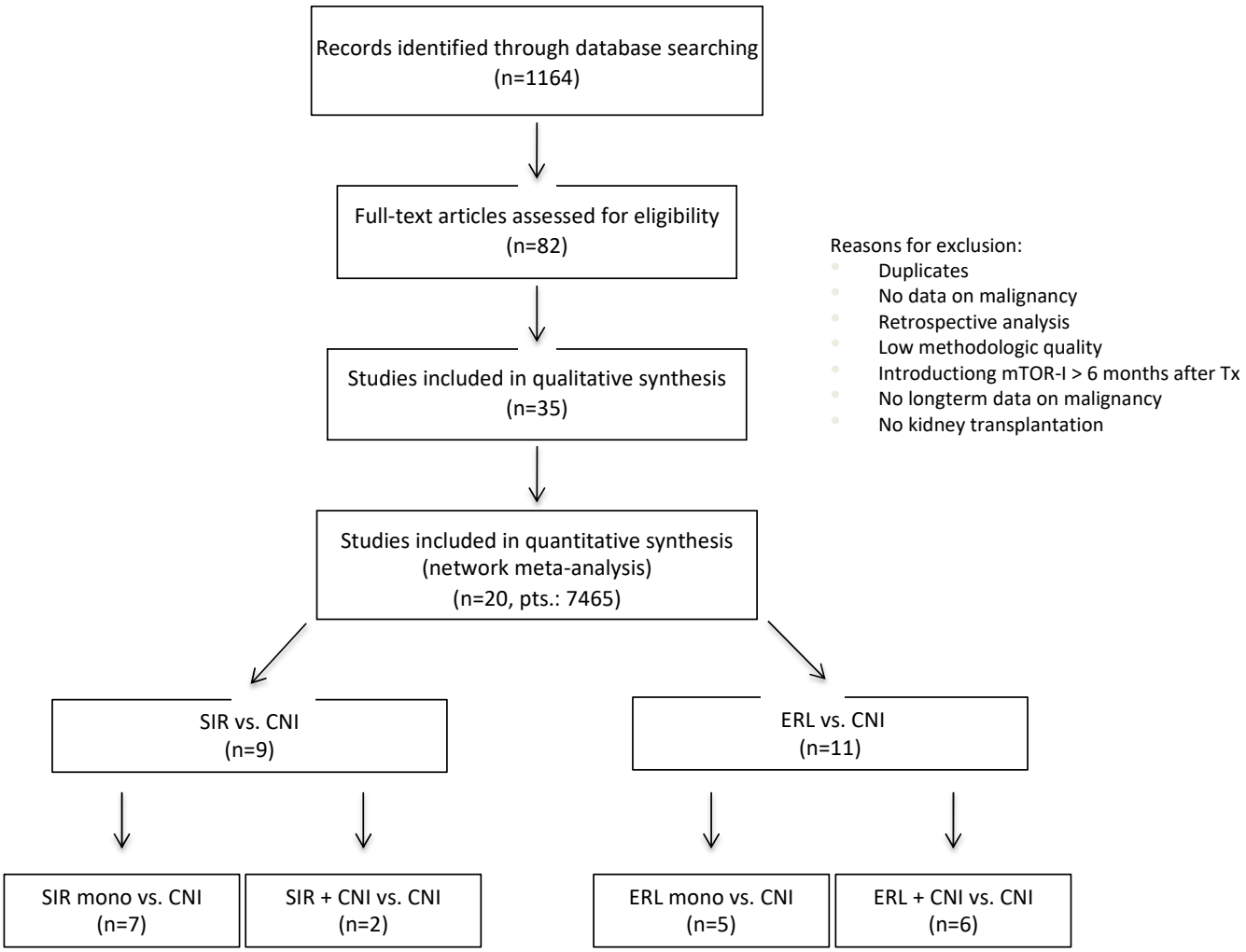
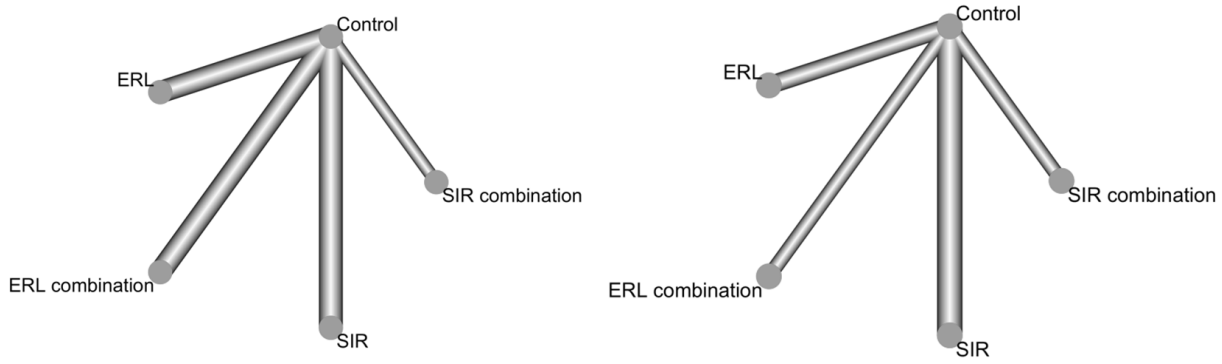


Figure 1. Flow chart of the selection of articles.

Among the RCTs using SIR, 7 compared SIR monotherapy and 2 compared the combination of SIR and CNI against a CNI treatment. For ERL, 5 trials compared monotherapy, while 6 trials compared the combination of ERL and CNI with CNI.

The included trials all showed data on the overall incidence of malignancies long-term post-transplantation. Of the 20 trials, only 13 (65%) showed data on the incidence of malignancies without NMSCs. The network graphs show the geometry of the two different treatment networks (Figure 2).



(**A**) (**B**)

Figure 2. Geometry of the treatment network. (**A**) Malignancy overall; (**B**) malignancy without NMSC (for the description of the network graph, please see the Materials and Methods section).

3.2. Methodologic Quality

All 20 RCTs were evaluated to have good methodological quality based on the Cochrane Collaboration tool (File S1, Supplementary Data). An ITT approach was employed in nearly all of the RCTs to analyze the data (19/20, 95%).

3.3. Incidence of Overall Malignancy Long-Term Post-Tx

All mTOR-Is were able to significantly reduce the relative risk for malignancy (NMSC included) compared to standard CNI treatment, as demonstrated in the network meta-analysis with random-effects. The combination therapy of SIR and CNI showed the strongest antitumoral effect of all analyzed treatments (RR 0.23, 95% CI [0.09, 0.55]; two RCTs). All other mTOR-I treatment regimens also displayed a significant reduction in relative risks (SIR monotherapy—seven RCTs; ERL monotherapy—five RCTs; ERL + CNI—six RCTs) (Figure 3).

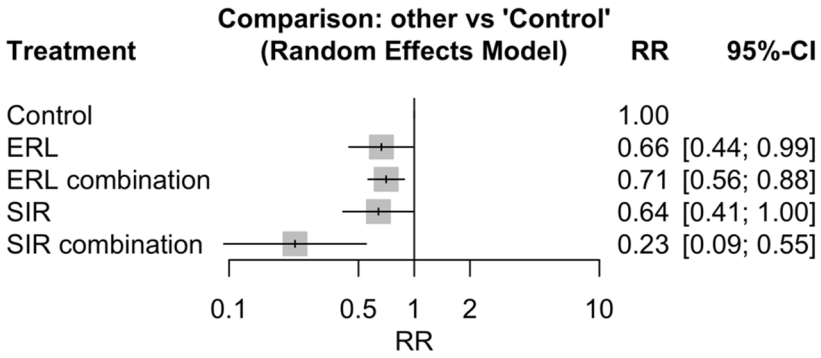


Figure 3. Forest plot showing the relative risks (RRs) of the incidence of overall malignancies (NMSC included) for the four mTOR-I vs. CNI treatment options after transplantation.

There was no within-design heterogeneity detected in the model (I^2 = 0% [0.0%; 50.0%], not significant (n.s.)). The network estimates between groups are shown in the net league table (Table 1).

Table 1. Overall malignancy (NMSC included). League table showing RRs and confidence interval.

ERL				
0.94 (0.59; 1.50)	ERL combination	.	.	
1.04 (0.57; 1.89)	1.10 (0.67; 1.81)	SIR	.	.
4.40 (1.82; 10.67)	3.11 (1.25; 7.74)	2.82 (1.05; 7.59)	SIR combination	.
0.66 (0.44; 0.99)	0.71 (0.56; 0.88)	0.64 (0.41; 1.00)	0.23 (0.09; 0.55)	Control

3.4. Incidence of Malignancy Without NMSCs Long-Term Post-Tx

The network meta-analysis with random effects showed that SIR-based immunosuppression compared to CNI could still significantly reduce the risk for malignancy when NMSCs were excluded (SIR + CNI − RR 0.25, 95% CI [0.07, 0.90]; two RCTs). Although the remaining mTOR-I treatment options were able to reduce the risk for malignancy, this effect was not significant (SIR monotherapy—six RCTs; ERL monotherapy—three RCTs; ERL + CNI—two RCTs) (Figure 4).

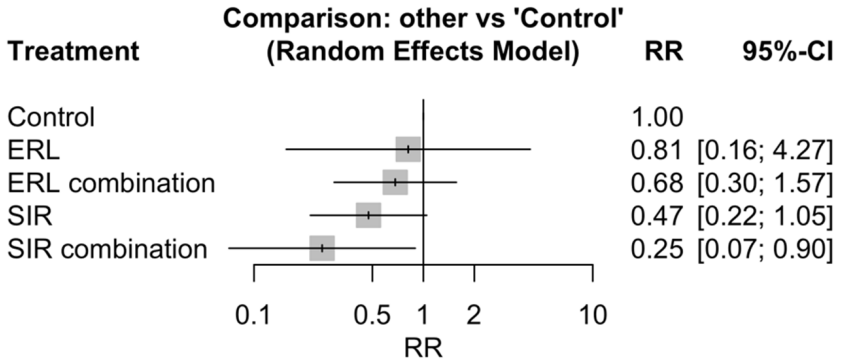


Figure 4. Forest plot showing the relative risks (RRs) of the incidence of overall malignancies without NMSCs on the four analyzed mTOR-I vs. CNI treatment options after transplantation.

A non-significant within-design heterogeneity was observed in the model (I^2 = 29.2% [0.0%; 66.1%], n.s.). The network estimates between groups are shown in the net league table (Table 2).

Table 2. Malignancy without NMSC. League table showing RRs and confidence interval.

ERL				
1.19 (0.19; 7.62)	ERL combination			
1.72 (0.27; 10.77)	1.44 (0.46; 4.53)	SIR		
3.22 (0.40; 25.97)	2.70 (0.59; 12.28)	1.88 (0.42; 8.36)	SIR combination	
0.81 (0.16; 4.27)	0.68 (0.30; 1.57)	0.47 (0.22; 1.05)	0.25 (0.07; 0.90)	Control

4. Discussion

This systematic review examines the impact of mTOR-Is compared to CNIs on malignancy following kidney transplantation. A network meta-analysis was used to estimate the antitumoral effect of four different mTOR-I-based regimens. This analysis included data of 20 RCTs involving 7465 patients in total, making it the largest study of its kind on this topic.

The longer immunosuppressants are used, the higher the risk of developing tumors. Thus, only long-term RCTs with a minimum follow up more than 24 months after transplantation were included.

Former reports have confirmed that mTOR-Is can reduce the incidence for malignancy. This effect has been shown, especially for NMSCs, multiple times [21–23]. The results of this network meta-analysis align with these studies, demonstrating that all mTOR-Is regimens provide a benefit in reducing the incidence of malignancy, including NMSCs. Clinical trials directly comparing SIR with ERL are missing, and to the best of our knowledge, none are currently being implemented. By using the statistical method of network analysis, we could show that the lowest relative risk for malignancy is under the combination therapy of SIR and CNI (RR 0.23). Monotherapy with SIR was also favorable compared to CNI (RR 0.64). Also, monotherapy of ERL (RR 0.66) and a combination of ERL and CNI (RR 0.71) showed significantly reduced relative risks for malignancy compared to CNI.

SIR (Rapamune) is produced from *Streptomyces hygroscopicus* as a macrolide antibiotic. With an additional hydroxyethyl group at the C (40), ERL (Certican) is a derivative of SIR. Both SIR and ERL bind to the same intracellular immunophilin (FKBP12) as TAC. However, rather than inhibiting calcineurin, the drug–receptor complex in this case binds to proteins called "mammalian targets of rapamycin" (mTOR). This leads to cell cycle arrest by inhibiting a multifunctional serine-threonine kinase, which in turn prevents both DNA and protein synthesis [24]. In comparison to SIR, ERL exhibits distinct tissue and subcellular distribution, varying affinities for active drug transporters and drug metabolizing enzymes, and a considerably higher potency in terms of interacting with the mTOR complex 2 (mTORC2) [25].

The antitumoral effect of mTOR-I can be explained by the following mechanisms: 1. An increase in E-cadherin promotes cellular junctions and thereby prevents tumor cell migration. 2. The increase in p-27kip-1 kinase inhibits cyclins, which are required for the cell cycle. 3. Reduction of IL-10 inhibits the Janus kinase transmitter, Jak-Stat transcription and cell growth. 4. Inhibition of mTOR serine-threonine-kinase decreases the proliferation of endothelial and smooth muscle cells (angiogenesis), T lymphocytes (anti-rejection activity), and neoplastic cells [26,27].

Why the combination of SIR and CNI and a therapy with SIR in general is favorable against the other regimens in our analysis, and which molecular mechanism underlies this difference, remain unknown. One reason for this could be that only two RCTs with the combination therapy of SIR and CNI showed results on malignancy, and thus could be included in this network analysis [28–31]. Both trials used induction therapy and mTOR-Is de novo. Because of this, the trial conducted by Kumar et al. had a very long follow-up of 96 months [30,31]. This could have led to a stronger antitumoral effect of the combination of SIR and CNI. Also, both studies had an early complete withdrawal of the additional corticosteroid medication. Using the combination, mTOR-I and CNI trough levels are substantially reduced. There is evidence that a reduction in immunosuppression may be an effective adjuvant therapeutic strategy in the case of malignancy [32].

Another indirect effect on tumor development can be the reduction in oncogenic viruses under a combination therapy of mTOR-I and CNI [15,33], which could have led to fewer malignancies in these RCTs.

Even though the anti-tumoral effect of the mTOR-Is seems to be especially potent against NMSCs, we and others have already shown that mTOR-Is also have a certain anti-tumor effect against other tumors [13,26,34,35]. The predominant part of the anti-tumor effect remained present even when administered in combination with a CNI [13]. We also tried to address the important question of whether patients under mTOR-I benefit regarding the incidence of tumors other than NMSCs. This beneficial effect could be confirmed in this

new network analysis, with a significant risk reduction only for the combination of SIR and CNI (RR 0.25).

A large metanalysis with 21 included RCTs showed that SIR was associated with a reduction in the risk of malignancy and NMSC in transplant recipients. The risk reduction was also seen when NMSCs were excluded [36]. Another metanalysis on patients after kidney transplantation confirmed the results of SIR on the incidence of NMSC but showed conflicting results for other tumors, with a reduced risk for kidney cancer but an elevated risk for prostate cancer [37]. This may be due to the inclusion of trials with a too-short follow up. Nearly 30% of the included trials had a maximum follow up of 12 months, averaging only 2 years follow up. This may have been simply too short to detect significant effects on tumor incidence.

The trials on ERL show similar results. ERL has been approved as an antitumoral agent for various malignant entities, such as advanced metastatic renal cell cancer [38,39], gastroenteropancreatic neuroendocrine tumors [40] and subependymal giant cell astrocytoma [41].

Furthermore, we cannot rule out the possibility that mTOR-Is may be permissive for certain tumor types while inhibiting others, as has been suggested for prostate and renal cancers [37].

Our study has some limitations. As highlighted above, there were only two trials comparing therapy with SIR and CNI with a CNI-alone therapy. This may have led to a bias in our results. Data on other malignancies than NMSC were reported in only 13 of the 20 analyzed trials (65%), with an average follow up of 46 months. For some tumors, 4 years of follow up might be too short.

Naturally, the primary endpoint in the included RCTs was on survival and biopsy proven acute rejection (BPAR) and not malignancy, and we did not have patient-level information from the included RCTs. Given the known association between immunosuppression and malignancy, this adverse event is likely to have been closely monitored and not missed during trial follow-up visits.

We also have to mention that we had to exclude a relevant RCT from Ekberg et al. on SIR versus CNI [42]. Of the 1589 patients initially included, only 958 (60%) were included in the follow-up group and only 533 were still on treatment after 3 years. Correspondingly, the numbers for the SIR group were 399 initial vs. 228 follow-up and 92 (40%) on treatment. Overall, 24% of patients on SIR were switched to tacrolimus in the first year. As we were interested in long-term tumor data, this is a relevant drop out which could have influenced this network analysis.

5. Conclusions

It is well known that an mTOR-I-based treatment in transplant patients reduces the risk of tumor manifestation in comparison to CNI treatment. A combination of SIR and CNI seems to be the most potent mTOR-I therapy against malignancies. SIR is not likely to experience a renaissance in solid organ transplantation. Nevertheless, trials like this are important to help understand the beneficial effects of mTOR-inhibition better.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/transplantology6010002/s1, File S1: Cochrane Collaboration tool assessing the methodological quality; Table S1: Included trials using SIR as the mTOR-I; Table S2: Included trials using ERL as the mTOR-I.

Author Contributions: Conceptualization, S.W. and J.A.; methodology, S.W. and S.S.; software, S.S.; validation, S.W., J.A. and S.S.; formal analysis, S.W. and S.S.; investigation, S.W., M.S. and F.S.; resources, S.W. and J.A.; data curation, S.W., M.L. and U.W.; writing—original draft preparation, S.W., S.S. and J.A.; writing—review and editing, F.S., M.S., M.L. and U.W.; visualization, S.W. and S.S.; supervision, J.A. and J.W.; project administration, J.W. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are available on request. A request for the data can be sent to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Tapiawala, S.N.; Tinckam, K.J.; Cardella, C.J.; Schiff, J.; Cattran, D.C.; Cole, E.H.; Kim, S.J. Delayed graft function and the risk for death with a functioning graft. *J. Am. Soc. Nephrol.* **2010**, *21*, 153–161. [CrossRef]
2. Wimmer, C.D.; Rentsch, M.; Crispin, A.; Illner, W.D.; Arbogast, H.; Graeb, C.; Jauch, K.W.; Guba, M. The janus face of immunosuppression—De novo malignancy after renal transplantation: The experience of the Transplantation Center Munich. *Kidney Int.* **2007**, *71*, 1271–1278. [CrossRef]
3. Domhan, S.; Zeier, M.; Abdollahi, A. Immunosuppressive therapy and post-transplant malignancy. *Nephrol. Dial. Transplant.* **2009**, *24*, 1097–1103. [CrossRef]
4. Penn, I. Occurrence of cancers in immunosuppressed organ transplant recipients. *Clin. Transplant.* **1998**, 147–158.
5. Opelz, G.; Dohler, B. Association of HLA mismatch with death with a functioning graft after kidney transplantation: A collaborative transplant study report. *Am. J. Transplant.* **2012**, *12*, 3031–3038. [CrossRef]
6. Webster, A.C.; Wong, G.; Craig, J.C.; Chapman, J.R. Managing cancer risk and decision making after kidney transplantation. *Am. J. Transplant.* **2008**, *8*, 2185–2191. [CrossRef]
7. Krynitz, B.; Edgren, G.; Lindelof, B.; Baecklund, E.; Brattstrom, C.; Wilczek, H.; Smedby, K.E. Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008—A Swedish population-based study. *Int. J. Cancer* **2013**, *132*, 1429–1438. [CrossRef]
8. Na, R.; Grulich, A.E.; Meagher, N.S.; McCaughan, G.W.; Keogh, A.M.; Vajdic, C.M. De novo cancer-related death in Australian liver and cardiothoracic transplant recipients. *Am. J. Transplant.* **2013**, *13*, 1296–1304. [CrossRef]
9. Na, R.; Grulich, A.E.; Meagher, N.S.; McCaughan, G.W.; Keogh, A.M.; Vajdic, C.M. Comparison of de novo cancer incidence in Australian liver, heart and lung transplant recipients. *Am. J. Transplant.* **2013**, *13*, 174–183. [CrossRef]
10. Engels, E.A.; Pfeiffer, R.M.; Fraumeni, J.F., Jr.; Kasiske, B.L.; Israni, A.K.; Snyder, J.J.; Wolfe, R.A.; Goodrich, N.P.; Bayakly, A.R.; Clarke, C.A.; et al. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA* **2011**, *306*, 1891–1901. [CrossRef]
11. Hojo, M.; Morimoto, T.; Maluccio, M.; Asano, T.; Morimoto, K.; Lagman, M.; Shimbo, T.; Suthanthiran, M. Cyclosporine induces cancer progression by a cell-autonomous mechanism. *Nature* **1999**, *397*, 530–534. [CrossRef] [PubMed]
12. O'Donovan, P.; Perrett, C.M.; Zhang, X.; Montaner, B.; Xu, Y.Z.; Harwood, C.A.; McGregor, J.M.; Walker, S.L.; Hanaoka, F.; Karran, P. Azathioprine and UVA light generate mutagenic oxidative DNA damage. *Science* **2005**, *309*, 1871–1874. [CrossRef]
13. Wolf, S.; Hoffmann, V.S.; Habicht, A.; Kauke, T.; Bucher, J.; Schoenberg, M.; Werner, J.; Guba, M.; Andrassy, J. Effects of mTOR-Is on malignancy and survival following renal transplantation: A systematic review and meta-analysis of randomized trials with a minimum follow-up of 24 months. *PLoS ONE* **2018**, *13*, e0194975. [CrossRef]
14. Hutton, B.; Salanti, G.; Caldwell, D.M.; Chaimani, A.; Schmid, C.H.; Cameron, C.; Ioannidis, J.P.; Straus, S.; Thorlund, K.; Jansen, J.P.; et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. *Ann. Intern. Med.* **2015**, *162*, 777–784. [CrossRef] [PubMed]
15. Wolf, S.; Hoffmann, V.S.; Sommer, F.; Schrempf, M.; Li, M.; Ryll, M.; Wirth, U.; Ilmer, M.; Werner, J.; Andrassy, J. Effect of Sirolimus vs. Everolimus on CMV-Infections after Kidney Transplantation-A Network Meta-Analysis. *J. Clin. Med.* **2022**, *11*, 4216. [CrossRef] [PubMed]
16. Gerta Rücker, U.K.; König, J.; Efthimiou, O.; Davies, A.; Papkonstantinou, T.; Schwarzer, G. *Network Meta-Analysis Using Freuquentist Methods*, Version 2.1-0. 2022.
17. Higgins, J.P.; Thompson, S.G. Quantifying heterogeneity in a meta-analysis. *Stat. Med.* **2002**, *21*, 1539–1558. [CrossRef]

18. Julian, P.T.; Higgins, S.G. Cochrane Handbook for Systematic Reviews of Interventions. T. C. Collaboration. 2008. Available online: https://handbook-5-1.cochrane.org (accessed on 14 May 2022).
19. Doug Altman, D.A.; Bender, R.; Bunce, C.; Campbell, M.; Clarke, M.; Deeks, J.; Gates, S.; Higgins, J.; Pace, N.; Thompson, S. Chapter 16: Special topics in statistics. In *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Updated March 2011)*; The Cochrane Collaboration: London, UK, 2011.
20. Pengel, L.H.; Barcena, L.; Morris, P.J. The quality of reporting of randomized controlled trials in solid organ transplantation. *Transplant. Int.* **2009**, *22*, 377–384. [CrossRef]
21. Ghazal, K.; Stenard, F.; Dahlqvist, G.; Barjon, C.; Aoudjehane, L.; Scatton, O.; Conti, F. Treatment with mTOR inhibitors after liver transplantation enables a sustained increase in regulatory T-cells while preserving their suppressive capacity. *Clin. Res. Hepatol. Gastroenterol.* **2018**, *42*, 237–244. [CrossRef]
22. Thomson, A.W.; Turnquist, H.R.; Raimondi, G. Immunoregulatory functions of mTOR inhibition. *Nat. Rev. Immunol.* **2009**, *9*, 324–337. [CrossRef]
23. Gluck, M.; Hodak, E.; Davidovici, B. Mammalian target of rapamycin inhibitors for prolonged secondary prevention of non-melanoma skin cancer in solid organ transplant recipients. *Dermatol. Ther.* **2022**, *35*, e15649. [CrossRef]
24. Webster, A.C.; Lee, V.W.; Chapman, J.R.; Craig, J.C. Target of rapamycin inhibitors (TOR-I; sirolimus and everolimus) for primary immunosuppression in kidney transplant recipients. *Cochrane Database Syst. Rev.* **2006**, CD004290. [CrossRef]
25. Klawitter, J.; Nashan, B.; Christians, U. Everolimus and sirolimus in transplantation-related but different. *Expert. Opin. Drug Saf.* **2015**, *14*, 1055–1070. [CrossRef]
26. Salvadori, M. Antineoplastic effects of mammalian target of rapamycine inhibitors. *World J. Transplant.* **2012**, *2*, 74–83. [CrossRef]
27. de Fijter, J.W. Cancer and mTOR Inhibitors in Transplant Recipients. *Transplantation* **2017**, *101*, 45–55. [CrossRef]
28. Kandaswamy, R.; Melancon, J.K.; Dunn, T.; Tan, M.; Casingal, V.; Humar, A.; Payne, W.D.; Gruessner, R.W.; Dunn, D.L.; Najarian, J.S.; et al. A prospective randomized trial of steroid-free maintenance regimens in kidney transplant recipients--an interim analysis. *Am. J. Transplant.* **2005**, *5*, 1529–1536. [CrossRef]
29. Suszynski, T.M.; Gillingham, K.J.; Rizzari, M.D.; Dunn, T.B.; Payne, W.D.; Chinnakotla, S.; Finger, E.B.; Sutherland, D.E.R.; Najarian, J.S.; Pruett, T.L.; et al. Prospective randomized trial of maintenance immunosuppression with rapid discontinuation of prednisone in adult kidney transplantation. *Am. J. Transplant.* **2013**, *13*, 961–970. [CrossRef]
30. Kumar, M.S.; Heifets, M.; Moritz, M.J.; Saeed, M.I.; Khan, S.M.; Fyfe, B.; Sustento-Riodeca, N.; Daniel, J.N.; Kumar, A. Safety and efficacy of steroid withdrawal two days after kidney transplantation: Analysis of results at three years. *Transplantation* **2006**, *81*, 832–839. [CrossRef]
31. Anil Kumar, M.S.; Irfan Saeed, M.; Ranganna, K.; Malat, G.; Sustento-Reodica, N.; Kumar, A.M.; Meyers, W.C. Comparison of four different immunosuppression protocols without long-term steroid therapy in kidney recipients monitored by surveillance biopsy: Five-year outcomes. *Transpl. Immunol.* **2008**, *20*, 32–42. [CrossRef]
32. Otley, C.C.; Maragh, S.L. Reduction of immunosuppression for transplant-associated skin cancer: Rationale and evidence of efficacy. *Dermatol. Surg.* **2005**, *31*, 163–168. [CrossRef]
33. Andrassy, J.; Hoffmann, V.S.; Rentsch, M.; Stangl, M.; Habicht, A.; Meiser, B.; Fischereder, M.; Jauch, K.W.; Guba, M. Is cytomegalovirus prophylaxis dispensable in patients receiving an mTOR inhibitor-based immunosuppression? a systematic review and meta-analysis. *Transplantation* **2012**, *94*, 1208–1217. [CrossRef]
34. Santos, A.H., Jr.; Chen, C.; Leghrouz, M.A.; Bueno, E.P.; Lee, J.J.; Wen, X. Association of HLA mismatch and MTOR inhibitor regimens with malignancy and mortality after kidney transplantation. *Transpl. Immunol.* **2021**, *66*, 101391. [CrossRef] [PubMed]
35. Dumortier, J.; Maucort-Boulch, D.; Poinsot, D.; Thimonier, E.; Chambon-Augoyard, C.; Ducroux, E.; Vallin, M.; Walter, T.; Robinson, P.; Guillaud, O.; et al. Immunosuppressive regimen and risk for de novo malignancies after liver transplantation for alcoholic liver disease. *Clin. Res. Hepatol. Gastroenterol.* **2018**, *42*, 427–435. [CrossRef]
36. Knoll, G.A.; Kokolo, M.B.; Mallick, R.; Beck, A.; Buenaventura, C.D.; Ducharme, R.; Barsoum, R.; Bernasconi, C.; Blydt-Hansen, T.D.; Ekberg, H.; et al. Effect of sirolimus on malignancy and survival after kidney transplantation: Systematic review and meta-analysis of individual patient data. *BMJ* **2014**, *349*, g6679. [CrossRef]
37. Yanik, E.L.; Siddiqui, K.; Engels, E.A. Sirolimus effects on cancer incidence after kidney transplantation: A meta-analysis. *Cancer Med.* **2015**, *4*, 1448–1459. [CrossRef]
38. Oyama, M.; Sugiyama, T.; Nozawa, M.; Fujimoto, K.; Kishida, T.; Kimura, G.; Tokuda, N.; Hinotsu, S.; Shimozuma, K.; Akaza, H.; et al. Efficacy and safety of sequential use of everolimus in Japanese patients with advanced renal cell carcinoma after failure of first-line treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitor: A multicenter phase II clinical trial. *Jpn. J. Clin. Oncol.* **2017**, *47*, 551–559. [CrossRef]
39. Motzer, R.J.; Escudier, B.; Oudard, S.; Hutson, T.E.; Porta, C.; Bracarda, S.; Grunwald, V.; Thompson, J.A.; Figlin, R.A.; Hollaender, N.; et al. Efficacy of everolimus in advanced renal cell carcinoma: A double-blind, randomised, placebo-controlled phase III trial. *Lancet* **2008**, *372*, 449–456. [CrossRef]

40. Yao, J.C.; Shah, M.H.; Ito, T.; Bohas, C.L.; Wolin, E.M.; Van Cutsem, E.; Hobday, T.J.; Okusaka, T.; Capdevila, J.; de Vries, E.G.; et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N. Engl. J. Med.* **2011**, *364*, 514–523. [CrossRef]
41. Franz, D.N.; Belousova, E.; Sparagana, S.; Bebin, E.M.; Frost, M.; Kuperman, R.; Witt, O.; Kohrman, M.H.; Flamini, J.R.; Wu, J.Y.; et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): A multicentre, randomised, placebo-controlled phase 3 trial. *Lancet* **2013**, *381*, 125–132. [CrossRef]
42. Ekberg, H.; Tedesco-Silva, H.; Demirbas, A.; Vitko, S.; Nashan, B.; Gurkan, A.; Margreiter, R.; Hugo, C.; Grinyo, J.M.; Frei, U.; et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *N. Engl. J. Med.* **2007**, *357*, 2562–2575. [CrossRef]