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Review – Kidney Cancer

A Systematic Review and Meta-analysis Comparing the Effectiveness and Adverse Effects of Different Systemic Treatments for Non-clear Cell Renal Cell Carcinoma

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Abstract

Context: While vascular endothelial growth factor-targeted therapy and mammalian target of rapamycin inhibition are effective strategies in treating clear cell renal cell carcinoma (ccRCC), the most effective therapeutic approach for patients with non-clear cell RCC (non-ccRCC) is unknown.
Objective: To systematically review relevant literature comparing the oncological outcomes and adverse events of different systemic therapies for patients with metastatic non-ccRCC.
Evidence acquisition: Relevant databases including MEDLINE, Embase, and the Cochrane Library were searched up to March 24, 2016. Only comparative studies were included. Risk of bias and confounding assessments were performed. A meta-analysis was planned for and only performed if methodologically appropriate; otherwise, a narrative synthesis was undertaken.
Evidence synthesis: The literature search identified 812 potential titles and abstracts. Five randomized controlled trials, recruiting a total of 365 patients, were included. Three studies compared sunitinib against everolimus, one of which reported the results for non-ccRCC as a subgroup rather than as an entire randomized cohort. Individually, the studies showed a trend towards favoring sunitinib in terms of overall survival and progression-free survival (PFS; Everolimus versus Sunitinib in Patients with Metastatic Non-clear Cell Renal Cell Carcinoma hazard ratio [HR]: 1.41, 80% confidence interval [CI]

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1.03–1.92 and 1.41, 95% CI: 0.88–2.27, Evaluation in Metastatic Non-clear Cell Renal Cell Carcinoma HR: 1.16, 95% CI: 0.67–2.01, Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-line and Second-line Treatment of Patients with Metastatic Renal Cell Carcinoma HR: 1.5, 95% CI: 0.9–2.8), but this trend did not reach statistical significance in any study. Meta-analysis was performed on two studies which solely recruited patients with non-ccRCC reporting on PFS, the results of which were inconclusive (HR: 1.30, 95% CI: 0.91–1.86). Sunitinib was associated with more Grade 3–4 adverse events than everolimus, although this was not statistically significant.

Conclusions: This systematic review and meta-analysis represent a robust summary of the evidence base for systemic treatment of metastatic non-ccRCC. The results show a trend towards favoring vascular endothelial growth factor-targeted therapy for PFS and overall survival compared with mammalian target of rapamycin inhibitors, although statistical significance was not reached. The relative benefits and harms of these treatments remain uncertain. Further research, either in the form of an individual patient data meta-analysis involving all relevant trials, or a randomized controlled trial with sufficient power to detect potential differences between treatments, is needed.

Patient summary: We examined the literature to determine the most effective treatments for advanced kidney cancer patients whose tumors are not of the clear cell subtype. The results suggest that a drug called sunitinib might be more effective than everolimus, but the statistics supporting this statement are not yet entirely reliable. Further research is required to clarify this unmet medical need.

1. Introduction

Renal cell carcinoma (RCC) accounts for approximately 2–3% of all malignancies with variations in regional incidence ranging from 10–31.4/100 person/yr in men [1]. While 15–17% of patients diagnosed with RCC are estimated to present with metastatic disease; in current nationwide cancer statistics, validated risk scores suggest that approximately 30% of nonmetastatic patients who underwent a nephrectomy will be diagnosed with metastasis within 5 yr of follow-up. For 2016, 62 700 new cases of kidney cancer are expected to occur in North America, although this figure does include cancer of the renal pelvis [2]. The predominant subtype is clear cell RCC (ccRCC; 80–90%) with all other subtypes collectively summarized as non-clear cell renal cancer (non-ccRCC). Among other rare subtypes 10–15% of all RCC account for the papillary and 4–5% for the chromophobe subtype. The burden of either synchronous or metachronous metastatic RCC is high, with approximately 38 000 patients being diagnosed annually in Europe based on the figures from 2012, among whom almost 8000 had non-ccRCC [3]. In contrast to ccRCC, metastatic non-ccRCC is less responsive to vascular endothelial growth factor (VEGF)-targeted therapy or inhibitors of the mammalian target of rapamycin (mTOR). A recent systematic review compared the non-ccRCC subpopulation from pivotal randomized controlled trials (RCTs) with the predominant clear-cell population included in the same trials [4]. However, amongst patients with non-ccRCC, the relative benefits and detriments of each drug remain unclear. Meanwhile, two RCTs recruiting only non-ccRCC patients comparing VEGF-targeted therapy against mTOR inhibitors (Evaluation in Metastatic Non-clear Cell Renal Cell Carcinoma [ESPN] and Everolimus versus Sunitinib in Patients with Metastatic Non-clear Cell Renal Cell Carcinoma [ASPEN]) [5,6] and one RCT recruiting non-ccRCC and ccRCC patients comparing the same drugs but reporting the results for each subgroup separately (Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-line and Second-line Treatment of Patients with Metastatic Renal Cell Carcinoma [RECORD3]) [7] have reported their findings. The present systematic review was aimed at determining the effectiveness and harms of systemic therapy for non-ccRCC to determine the current evidence base and identify knowledge gaps.

2. Evidence acquisition

2.1. Search strategy

The review was undertaken by the European Association of Urology (EAU) RCC Guidelines Panel, which is a multidisciplinary panel consisting of expert urological surgeons, oncologists, pathologists, radiologists, and patient representation, as part of its guidelines update for 2016. The review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [8]. The search was conducted in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions [9]. Studies were identified by searching electronic databases and relevant websites. Highly sensitive electronic searches were conducted to identify published and ongoing comparative studies of systemic treatment of non-ccRCC. Searches were limited to studies published from 2000 onwards but no language restrictions were imposed. The search was complemented by additional sources, including relevant systematic reviews and the reference lists of included studies which were hand searched to identify additional potentially relevant studies. Additional reports were identified by a reference panel (EAU RCC Guidelines Panel).

The databases searched were MEDLINE (1946 to May 2016), MEDLINE In-process (March 24, 2016), Embase (1974 to March 24, 2016), Cochrane Controlled Trials

Register (The Cochrane Library, 2015), Science Citation Index (1970 to March 24, 2016), and Conference Proceedings Citation Index–Science (1990 to March 24, 2016). Systematic reviews and other background information were identified by searching the Cochrane Database of Systematic Reviews (The Cochrane Library, 2015). Additionally, clinicaltrials.gov and the World Health Organization International Clinical Trials Registry were searched to identify ongoing trials.

The search terms included kidney carcinoma, renal cell carcinoma, non-clear cell RCC, papillary RCC, papillary 1 RCC, papillary 2 RCC, chromophobe RCC, advanced RCC, metastatic RCC, cytoreductive nephrectomy, drug therapy, active surveillance, adjuvant chemotherapy, systemic therapy, sorafenib, sunitinib, bevacizumab, axitinib, pazopanib, everolimus, temsirolimus, interferon (IFN), interleukin 2, dovitinib, cabozantinib, tivozanib, tivantinib, erlotinib, placebo, randomized controlled trial. Full details of the protocol, search strategies used and websites consulted have been described in the Supplementary data.

Two reviewers (SFP and RT) screened all abstracts and full-text articles independently. Disagreement was resolved by discussion, and where no agreement was reached, a third independent party (FH) acted as an arbiter.

2.2. Types of study design included

RCTs, quasi-RCTs, and nonrandomized comparative studies were eligible for inclusion with no minimum number of patients and no language restrictions. Studies with no comparative elements were excluded. Studies with mixed populations (eg, non-ccRCC and ccRCC) were included if results were reported separately for the non-ccRCC subgroup. Studies that did not report each subgroup separately, were still included if the non-ccRCC subgroup represented at least 90% of the patient cohort.

2.3. Types of participants included

The study population consisted of patients diagnosed with non-ccRCC with metastatic disease receiving systemic therapy. Patients who had or did not have cytoreductive nephrectomy were included. Treatment-naïve patients, as well as patients undergoing second-line or third-line treatments, were included. Data on non-ccRCC subtypes were included, if available.

2.4. Types of interventions included

The agents considered included: sunitinib, sorafenib, axitinib, pazopanib, dovitinib, cabozantinib, tivantinib, erlotinib, bevacizumab, interleukin-2, IFN-α, 5-fluorouracil, and other different systemic treatments if identified during the search. Valid eligible comparators included any of the prespecified systemic therapy agents, placebo, active surveillance, or any other unspecified agent judged to be important by the reviewer. To be eligible for inclusion, studies must have included at least one of the prespecified systemic treatment agents.

2.5. Types of outcome measures included

The primary outcomes were OS, progression-free survival (PFS), and, where possible, response rate following the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Secondary outcomes included adverse events reported individually or collectively (eg, based on severity grading systems).

2.6. Data extraction

A data extraction form was developed a priori specifically to collect information on study design, characteristics of participants, characteristics of interventions, outcome measures, and risk of bias (RoB) or confounding. Two reviewers (SFP and RT) independently extracted data relating to the prespecified outcomes. Missing, unclear, or important additional data were requested from primary study authors.

2.7. Assessment of RoB and confounders

The standard Cochrane Collaboration risk of bias tool [9] was used to assess RoB in RCTs. For nonrandomized comparative studies, a modified RoB tool was used [10], incorporating additional domains based on confounding. The main confounders identified included age, subtype, performance status, and prognostic scores as well as lines of therapy (Supplementary data).

2.8. Data analysis

For data analysis, descriptive statistics were used to summarize baseline characteristics data. A quantitative synthesis (ie, meta-analysis) was performed only on RCTs, and only if methodologically appropriate. The random-effects model was used due to the anticipated clinical heterogeneity of participants and interventions. For time-to-event data, hazard ratios (HR) and 95% confidence intervals (CIs) obtained directly from studies were used to compare results, using the inverse variance method. Statistical heterogeneity between studies was assessed by visual inspection of plots of the data, the chi-square test for heterogeneity, and the I^2 statistic. Analysis was performed using Cochrane RevMan version 5.2 software (Cochrane Tech, London, UK). Where meta-analysis was not feasible, a narrative synthesis was provided instead, incorporating data on HR and 95% CIs and median OS or PFS for time-to-event data, and proportions (%) for categorical data (eg, response rate and adverse events). Data was presented for non-ccRCC as a group, and for distinct non-ccRCC subtypes, including papillary and chromophobe RCC, if available.

3. Evidence synthesis

3.1. Quantity of evidence identified

Eight-hundred and twelve (812) articles were identified by the literature search. Of these, 246 studies were eligible for

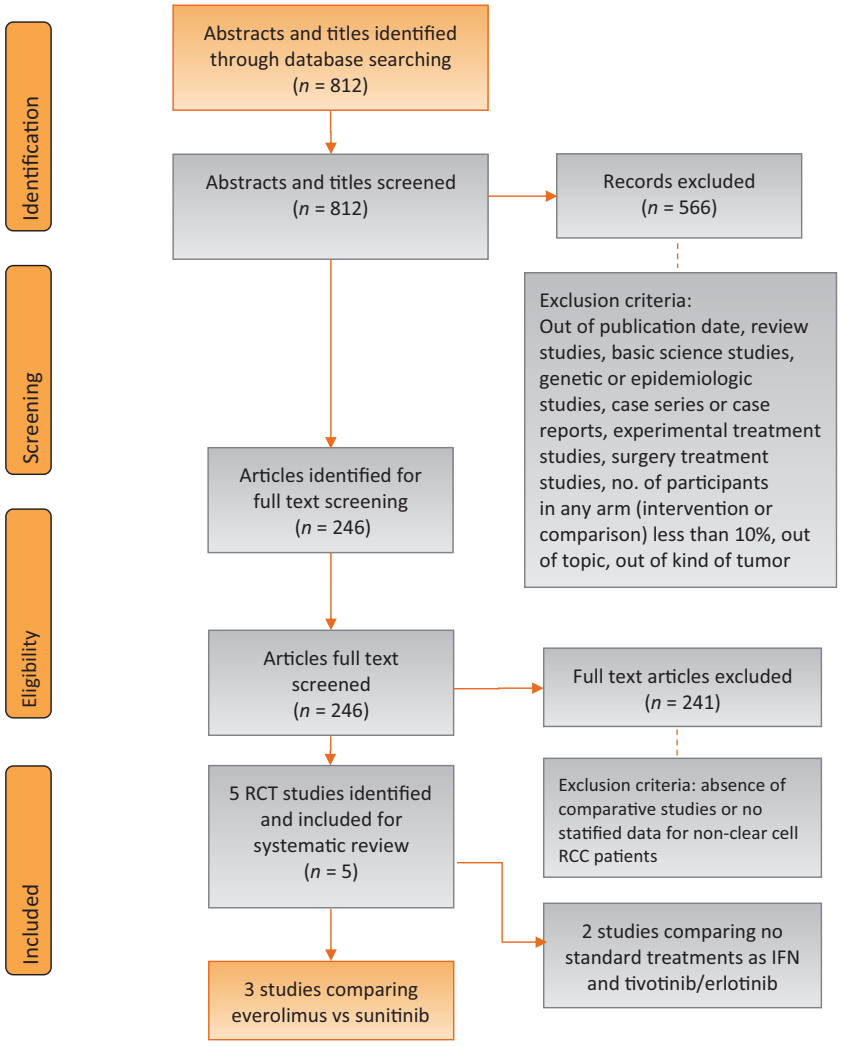

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart with the evidence synthesis. IFN = interferon; RCC = renal cell carcinoma; RCT = randomized controlled trial.

full text screening. Five studies (all RCTs) met the inclusion criteria and were included for evidence synthesis. There were no eligible nonrandomized comparative studies. Figure 1 represents the Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram outlining the study selection process. Unpublished data from the ESPN Trial [6] regarding PFS (HR and 95% CI) were kindly provided by Dr. Nizar M. Tannir.

3.2. *Characteristics of the included studies*

Five RCTs recruiting a total of 365 patients (258 with papillary histology and 40 with chromophobe histology) were included. Length of follow-up was not equally reported in the studies, but, when available, the median follow-up varied from 13 mo to 23.6 mo. All of these RCTs were multi-center studies. Three studies recruited exclusively non-ccRCC patients [5,6,11], whilst two studies recruited ccRCC and non-ccRCC patients but reported separate results for each subgroup [7,12]. Two studies [5,6] compared sunitinib versus everolimus for first-line treatment of patients with metastatic non-ccRCC. One study [7] compared sunitinib versus everolimus for first-line treatment of patients with metastatic ccRCC and non-ccRCC, and presented a posthoc analysis of the non-ccRCC subgroup. One study [11] compared tivantinib versus tivantinib in combination with erlotinib for patients with advanced and metastatic papillary RCC, based on the rationale that combining the epidermal growth factor receptor inhibitor erlotinib with tivantinib, a nonadenosine triphosphate competitive inhibitor of mesenchymal-epithelial transition factor (MET), may increase effectivity. Finally, one study [12] compared IFN alone versus temsirolimus alone versus temsirolimus in combination with IFN in patients with previously untreated advanced RCC, and reported a subgroup analysis of patients with non-ccRCC histology. The five studies recruited patients from: USA, UK and Canada (ASPEN), USA (ESPN), America, Australia, Asia, and Europe (RECORD3), USA (Southwest Oncology Group [SWOG]1107), America, Australia, Asia, Africa, and Europe [12]. The baseline characteristics of all included studies are outlined in Table 1.

Table 1 – General characteristics of the included studies

	Identificator	Population	Patients (*n*)	Non-clear cell histology subgroups	Line	Comparator
Armstrong (2015), [5]	ASPEN NCT01108445	Non-clear cell	108	Papillary 76/108 Chromophobe 16/108 Unclassified	First	Everolimus vs sunitinib
Tannir (2014), [6]	ESPN NCT01185366	Non-clear cell	68	Papillary 27/68 Chromophobe 12/68 Translocational Unclassified Sarcomatoid	First Second	Everolimus vs sunitinib
Motzer (2014), [7]	RECORD3 NCT00903175	Clear cell + non-clear cell	66	Papillary 50/66 Chromophobe 12/66 Unclassified	First Second	Everolimus vs sunitinib
Twardowski (2015), [11]	SWOG1107 NCT01688973	Non-clear cell	50	Papillary 50/50	First Second	Tivantininb vs tivantinib + erlotinib
Dutcher (2009), [12]	ARCC NCT00065468	Clear cell + non-clear cell	73	Papillary 55/73 Unclassified	First	IFN-α vs temsirolimus

ARCC = Applied Research in Cancer Control; ASPEN = Everolimus versus Sunitinib in Patients with Metastatic Non-clear Cell Renal Cell Carcinoma; ESPN = Evaluation in Metastatic Non-clear Cell Renal Cell Carcinoma; RECORD3 = Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-line and Second-line Treatment of Patients with Metastatic Renal Cell Carcinoma; SWOG = Southwest Oncology Group.

3.3. *RoB assessment of the included studies*

Overall, the RoB across studies was low to moderate, as summarized in Figure 2. All included studies were of prospective, randomized, and comparative design. The blinding of the studies was open label, with all arms containing active treatment. Only the ASPEN trial described an independent and external interpretation of the data.

3.4. *Comparisons of interventions results*

The summary of findings of all included studies concerning the main study outcomes are outlined in Table 2.

3.4.1. *Sunitinib versus everolimus*

3.4.1.1. OS. Data on OS were reported by the ESPN and ASPEN trials. The median OS for the sunitinib and everolimus groups was 16.2 mo versus 14.9 mo, and 31.5 mo versus 13.2 mo, for ESPN and ASPEN trials, respectively. The HR and 95% CI for ASPEN was 1.12 (95% CI: 0.7–2.1); data was not reported for ESPN.

3.4.1.2. PFS. All three studies (ESPN, ASPEN, and RECORD3) reported PFS data. The median PFS for sunitinib and everolimus groups was 6.1 mo versus 4.1 mo for ESPN; 8.3 mo versus 5.6 mo for ASPEN; and 7.2 mo versus 5.1 mo for RECORD3. The HR and 95% CI for ESPN was 1.16 (95% CI: 0.67–2.01). For ASPEN, the reported HR and 80% CI was 1.41 (80% CI: 1.03–1.92); the equivalent derived HR and 95% CI was 1.41 (95% CI: 0.88–2.26). For RECORD3, the HR and 95% CI was 1.5 (95% CI: 0.9–2.8). These results are summarized in Figure 3.

The data for PFS from two studies (ESPN and ASPEN) were suitable for meta-analysis (Fig. 4). The results of RECORD3 were not included in this meta-analysis because of methodological heterogeneity, since the non-ccRCC cohort was merely a subgroup of the randomized population, and the results for this subgroup were reported posthoc. The pooled HR was 1.30 (95% CI: 0.91–1.86, p = 0.15), indicating a trend for the superiority of sunitinib over everolimus in terms of PFS, although the results failed to reach statistical significance. No statistical heterogeneity was observed amongst the studies (I^2 = 0%).

3.4.1.3. Response rate. Data for response rate according to the RECIST criteria were reported in ESPN and ASPEN. Complete response (CR) rates for sunitinib and everolimus were 0 versus 0, and 0 versus 1, respectively. Partial response (PR) rates were 3 versus 1, and 9 versus 4, respectively. Stable disease rates were 21 versus 24, and 30 versus 30, respectively, whilst progressive disease rates were 9 versus 8, and 10 versus 13, respectively.

3.4.1.4. Adverse events. ESPN and ASPEN reported a Grade 3–4 toxicity rate for sunitinib and everolimus of 88% versus 54% and 78% versus 60%, respectively. Taking both studies together, the most common Grade 3–4 adverse events for sunitinib were hypertension (22 patients), fatigue (15 patients), diarrhea (13 patients), thrombocytopenia (eight patients), and neutropenia (seven patients), whilst for everolimus they were anemia (11 patients), fatigue (eight patients), pneumonitis (five patients), and stomatitis (five patients).

3.4.2. *Tivantinib versus tivantinib and erlotinib*

3.4.2.1. OS. Data on OS were reported by the SWOG1107 trial. The median OS for the tivantinib and tivantinib and erlotinib groups was 10.3 mo versus 11.3; p = 0.63. The HR and 95% CIs were not available.

3.4.2.2. PFS. SWOG1107 reported data on PFS. The median PFS for tivantinib and tivantinib and erlotinib groups was 2 mo versus 5.4 mo. The latest reported data based on ASCO 2015 were 2 mo versus 3.3 mo, p = 0.13, these data differ from the information previously reported [11]. The HR and 95% CI were not available.

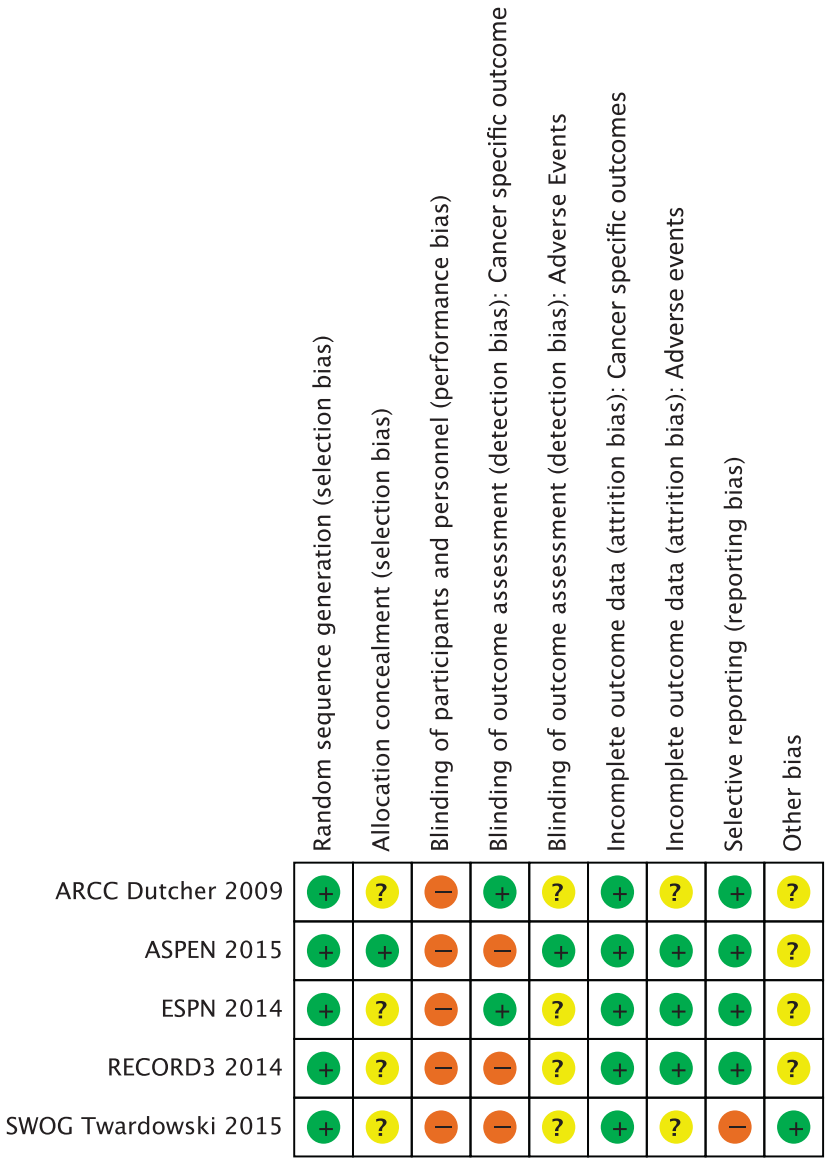

Fig. 2 – Risk of bias table with the five studies included in the systematic review.
Green point (+) = low risk of bias; yellow point (?) = unclear risk of bias; red point (–) = high risk of bias.
ARCC = Applied Research in Cancer Control; ASPEN = Everolimus versus Sunitinib in Patients with Metastatic Non-clear Cell Renal Cell Carcinoma; ESPN = Evaluation in Metastatic Non-clear Cell Renal Cell Carcinoma; RECORD3 = Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-line and Second-line Treatment of Patients with Metastatic Renal Cell Carcinoma; SWOG = Southwest Oncology Group.

3.4.2.3. Response rate and adverse events. The response rate for both arms was 0. SWOG1107 reported Grade 3 or superior toxicity for tivantinib and tivantinib and erlotinib of 28% (7/25) versus 52% (13/25); Grade 4: 4% (1/25) versus 4% (1/25); and Grade 5: 0% (0/25) versus 4% (1/25), respectively. The most frequent adverse events were fatigue, nausea and anemia in arm 1 (tivantinib); for arm 2 (tivantinib and erlotinib) they were rash, nausea, fatigue, and dyspnea. The *p* values were not reported by authors.

3.4.3. IFN versus temsirolimus

3.4.3.1. OS. Data on OS were reported by Dutcher et al [12] from the Applied Research in Cancer Control (ARCC) trial. The median OS for the IFN and temsirolimus groups was 4.3 mo versus 11.6 mo, calculated $p = 0.01$. The HR and 95% CI were: 0.49 (95% CI: 0.29–0.85).

3.4.3.2. PFS. Only ARCC reported PFS data. The median PFS for IFN and temsirolimus groups was 1.8 mo versus 7 mo, calculated $p = 0.0001$. The HR and 95% CI were 0.38 (95% CI: 0.23–0.62).

3.4.3.3. Response rate. Data for response rate according to RECIST criteria were reported in ARCC, but in the manuscript the results were recorded as follows: CR and PR, defined as *objective response*, in three patients for IFN and

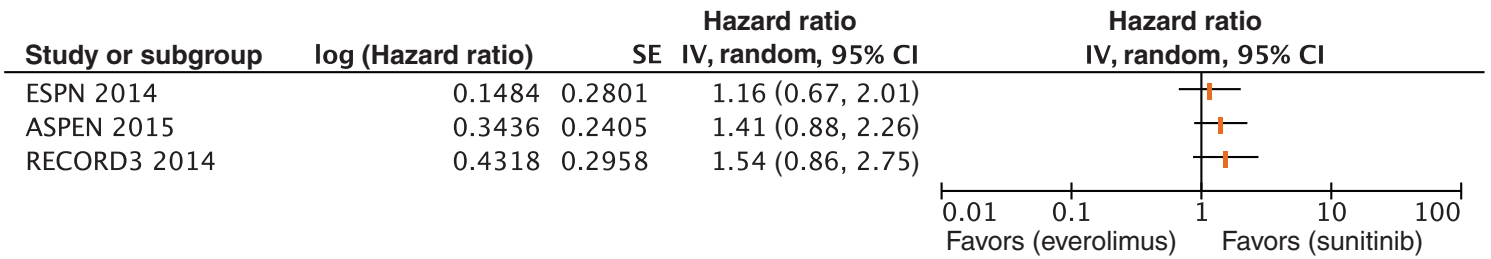

Fig. 3 – Forest plot comparing everolimus versus sunitinib first line (progression-free survival data) for Evaluation in Metastatic Non-clear Cell Renal Cell Carcinoma (ESPN), Applied Research in Cancer Control; ASPEN = Everolimus versus Sunitinib in Patients with Metastatic Non-clear Cell Renal Cell Carcinoma (ASPEN), and Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-line and Second-line Treatment of Patients with Metastatic Renal Cell Carcinoma (RECORD3).
CI = confidence interval; IV = instrumental variables; SE = standard error.

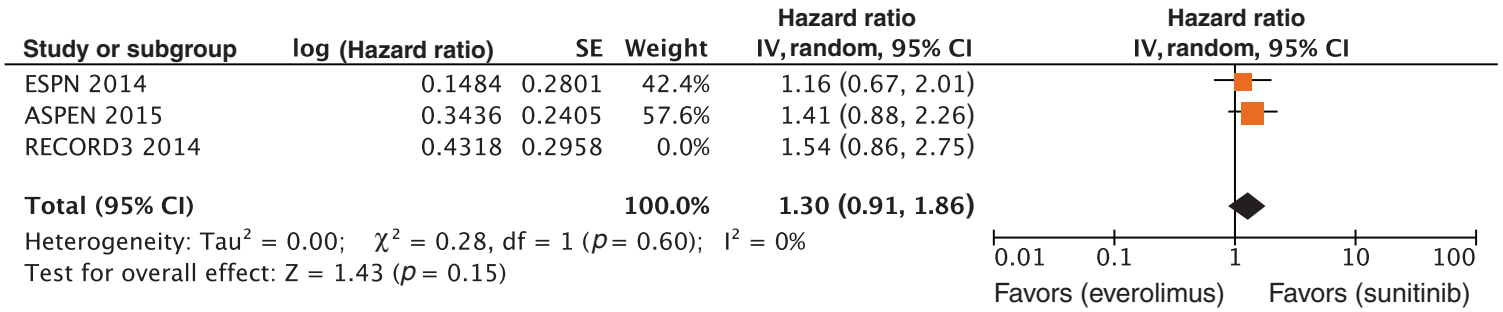

Fig. 4 – Forest plot and meta-analysis comparing everolimus versus sunitinib first line (progression-free survival data) for Evaluation in Metastatic Non-clear Cell Renal Cell Carcinoma (ESPN) and Everolimus versus Sunitinib in Patients with Metastatic Non-clear Cell Renal Cell Carcinoma (ASPEN).
CI = confidence interval; df = degrees of freedom; IV = instrumental variables; RECORD3 = Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-line and Second-line Treatment of Patients with Metastatic Renal Cell Carcinoma; SE = standard error.

Table 2 – Summary of main outcomes and harms of the included studies: overall survival (OS), progression-free survival (PFS), Response Evaluation Criteria in Solid Tumors (RECIST), and toxicity

RCT	Comparator	Age (range)	Sex, male/ female	Patients non-clear RCC (*n*)	Non-clear RCC (%)	OS (mo)	OS HR	PFS (mo)	PFS HR	Response RECIST (*n*)	Toxicity Grades 3–4	Toxicity Grade 3–4 types
ESPN first line	Everolimus	58 (23–73)	24/11	35	100	14.9 95% CI (8–23.4)	—	4.1 95% CI (2.7–10.5)	1.16 95% CI (0.67–2.01)	CR: 0 PR: 1 SD: 24 PD: 8	54%	Anemia: 5/35 Fatigue: 2/35
	Sunitinib	60 (28–76)	19/14	33		16.2 95% CI (14.2–NA)		6.1 95% CI (4.2–9.4)		CR: 0 PR: 3 SD: 21 PD: 9	88%	Fatigue 13/33 Hypertension 9/33 Diarrhea 8/33 Neutropenia 4/33
ASPEN	Everolimus	59 (29–90)	44/13	57	100	13.2 95% CI (9.7–37.9)	1.12 95% CI (0.7–2.)	5.6 80% CI (5.5–60)	1.41 80% CI (1.03–1.92) 1.41 95% CI (0.88–2.27)	CR: 1 PR: 4 SD: 30 PD: 13	60%	Anemia 6/57 Stomatitis 5/57
	Sunitinib	64 (24–100)	37/14	51		31.5 95% CI (14.8–NA)		8.3 80% CI (5.8–11.4)		CR: 0 PR: 9 SD: 30 PD: 10	78%	Hypertension 13/51 Infection 6/51 Diarrhea 5/51 Thrombocytopenia 4/51
RECORD3 first line	Everolimus	62 (20–89)[b]	166/72[b]	31	13	—[a]	—	5.1 Range (2.6–7.9)	1.5 95% CI (0.9–2.8)	—[a]	—[a]	—[a]
	Sunitinib	62 (29–84)[b]	176/57[b]	35	15	—[a]		7.2 Range (5.4–13.8)		—[a]	—[a]	—[a]
ARCC	Interferon-α	61	25/11	36	17	4.3 95% CI (3.2–7.3)	0.49 95% CI (0.29–0.85)	1.8 95% CI (1.6–2.1)	0.38 95% CI (0.23–0.62)	CR+PR: 3 CR+PR+SD: 3	—[a]	—[a]
	Temsirolimus	63	24/13	37	18	11.6 95% CI (8.9–13)		7 95% CI (3.9–8.9)		CR+PR: 2 CR+PR+SD: 15	—[a]	—[a]
SWOG1107	Tivantinib	64	34/16	25	100	10.3	—	2	—	RR: 0	32%	Anemia 2/25 Nausea 1/25 Neutropenia 1/25
	Tivantinib Erlotinib			25	100	11.3		5.4		RR: 0	56%	Rash 2/25 Transaminases 2/25 Anemia 1/25 Myocardial Infarction 1/25

No data available in meeting abstract.
ARCC = Applied Research in Cancer Control; ASPEN = Everolimus versus Sunitinib in Patients with Metastatic Non-clear Cell Renal Cell Carcinoma; CI = confidence interval; CR = complete response; ESPN = Evaluation in Metastatic Non-clear Cell Renal Cell Carcinoma; HR = hazard ratio; *n* = number; PD = progressive disease; PR = partial response; RCC = renal cell carcinoma; RCT = randomized controlled trial; RECORD3 = Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-line and Second-line Treatment of Patients with Metastatic Renal Cell Carcinoma; RR = response rate; SD = stable disease; SWOG = Southwest Oncology Group.
[a] There is not data specification for non-clear cell renal cell carcinoma population.
[b] Data from the general group (clear cell + non-clear cell).

three patients for temsirolimus, with a p value of 0.67. CR and PR and stable disease, defined as *clinical benefit*, in three patients for IFN and 15 patients for temsirolimus, with a p value of 0.002 between the two groups.

3.4.4. Systemic therapy in non-cc RCC subtypes

3.4.4.1. Papillary RCC. The ESPN and ASPEN trials presented the OS and PFS results for the papillary non-ccRCC subtype.

In ESPN, the OS results for 14 patients in the sunitinib arm and 13 patients in the everolimus arm were 16.6 mo (CI 95%: 5.9 to not applicable [NA]) and 14.9 mo (CI 95%: 7.1–22.7), respectively. In ASPEN, the data of OS was not given but it is mentioned in the text that no differences were noted within histology subset. The median PFS for sunitinib and everolimus groups was 5.7 mo versus 4.1 mo for ESPN; and 8.1 mo versus 5.5 mo for ASPEN with a 1.16 HR (80% CI: 1.1–2.3]. No further distinction was made between papillary type I and II subtypes.

SWOG1107 [11] compared tivantinib (ARQ-197) against tivantinib in combination with erlotinib, and presented the results for median OS and PFS for patients with papillary RCC. All the patients had papillary histology; consequently, the OS and PFS results have been previously reported in Section 3.4.2.

3.4.4.2. Chromophobe RCC. The ESPN and ASPEN trials presented the OS and PFS results for the chromophobe non-ccRCC subtype.

In ESPN, the OS results for six patients in the sunitinib arm and six patients in the everolimus arm were 31.6 mo (CI 95%: 14.2 to NA) and 25.1 mo (CI 95%: 4.7 to NA), respectively. In ASPEN, the data of OS was not given but it is mentioned in the text that no differences were noted within histology subset. The median PFS for sunitinib and everolimus groups was 8.9 mo versus NA for ESPN; and 5.5 mo versus 11.4 mo for ASPEN with a 0.7 HR (80% CI: 0.3–1.7).

3.5. Discussion

3.5.1. Principal findings

Our review identified five studies comparing different systemic therapies for patients with metastatic non-ccRCC. As such, the evidence base concerning the treatment of this group of patients is relatively small, although all included studies were RCTs. The majority of the identified studies (three out of five) compared sunitinib against everolimus [5–7]. The results of the three individual trials and a meta-analysis where the results of two studies were pooled showed no significant difference in PFS between the agents. However, a trend could be observed, favoring sunitinib. One study [11] compared tivantinib versus tivantinib plus erlotinib in patients with papillary histology, and concluded that tivantinib showed no clinical activity in patients with metastatic non-ccRCC. One other study [12] compared IFN versus temsirolimus and reported that IFN has less efficacy in patients with other RCC histology than in those with tumors of clear RCC histology; and temsirolimus appears to be efficacious in patients regardless of tumor histology.

3.5.2. Implications of review findings

For the comparison of sunitinib versus everolimus, two trials (ESPN and ASPEN) recruited only non-ccRCC patients. In the ESPN trial the alternative hypothesis was based on a PFS of 12 wk with sunitinib and 20 wk with everolimus [6]. However, the ESPN study closed early after an interim analysis based on data from 68 patients revealed that superiority would not be reached. In addition, ESPN included patients failing first-line therapy with either everolimus or sunitinib and crossing-over to second-line therapy with the alternating study agent [6]. This strategy is reminiscent of the RECORD3 design, which is a phase 2 RCT assessing first-line treatment of metastatic non-ccRCC with PFS as a primary endpoint, and comparing the sequencing of sunitinib followed by everolimus upon progression, versus everolimus followed by sunitinib upon progression, respectively [7]. In contrast to ASPEN and ESPN, all subtypes of RCC, including ccRCC and non-ccRCC, were eligible for inclusion in RECORD3. The analysis of non-ccRCC was prespecified and among the 402 patients included, 66 (16.4%) had non-ccRCC. Due to the heterogeneity of the RECORD3 trial, data from this study were not included in the meta-analysis. In addition, non-ccRCC is a heterogeneous disease entity. There was significant clinical heterogeneity between studies in terms of histological subtypes, lines of therapy, risk factors, and populations recruited, and this makes any comparisons across studies difficult to interpret. In both the ASPEN and RECORD3 studies, the majority of non-ccRCC were papillary subtypes (ie, 66% and 76%, respectively) [5,7]. Conversely, papillary RCC were a minority in the ESPN study, representing only 39.7% of the patients included [6]. In addition, ESPN enrolled 17.6% ccRCC sarcomatoid tumors which are not considered a non-ccRCC subtype in the International Consultation on Urological Diseases classification, and which have a reported poor prognosis [3]. This may have impacted on the median first-line PFS observed in ESPN with only 6.1 mo for sunitinib and 4.1 mo for everolimus, compared with 8.3 mo and 5.6 mo in ASPEN, and 7.2 mo and 5.1 mo in the RECORD3 non-ccRCC subgroup, respectively. When sarcomatoid tumors were excluded from the analysis, median OS with sunitinib was 31.6 mo versus 10.5 mo with everolimus ($p = 0.075$). A longer, but not statistically significant, median OS for sunitinib was also observed in the ASPEN study (31.5 mo vs 13.2 mo, HR 1.17, 95% CI: 0.65–2.14, $p = 0.6$). Despite the heterogeneity and risk of bias of these studies, it can be concluded that both agents only have modest effectiveness in non-ccRCC patients. Although not statistically significant, the studies suggest better effectiveness with sunitinib in terms of OS and PFS, at the cost of more frequent Grade 3-4 adverse events.

3.5.3. How the review findings compare with previous systematic reviews and clinical practice guidelines

Apart from a systematic review comparing effectiveness of targeted agents between ccRCC and non-ccRCC, no previous systematic review, nor meta-analysis has been performed comparing the effectiveness and adverse effects of systemic therapy for non-clear RCC. As a consequence, no recommendations regarding systemic treatment for patients with

non-ccRCC were given in previous EAU, American Urological Association, or National Comprehensive Cancer Network RCC guidelines. Based on this review and assessing the strength of recommendation according to the Grading of Recommendations Assessment, Development, and Evaluation Working Group principles [13], the EAU RCC Guidelines Panel has decided to recommend sunitinib over everolimus and temsirolimus for non-ccRCC in first-line (weak recommendation).

3.5.4. Future directions

The finding of a nonstatistical trend favoring sunitinib over everolimus for PFS is particularly compelling, and may be explained by the lack of statistical power inherently present in small exploratory studies. This issue may not have been satisfactorily resolved through a conventional meta-analysis, which merely presents a statistical *summary of summaries* based on averages. A potentially more useful approach is an individual patient data meta-analysis, whereby the data for all patients of all eligible studies (including RECORD3) can be combined at an individual level to provide a more accurate and reliable estimate of effectiveness and harmful effects [14]. At the same time, subgroup and sensitivity analysis, and tests of interactions, can be performed on relevant variables including histological subtypes and types and sequencing of treatment, to assess their impact on outcomes. The patients would likely benefit from this approach, since a clear recommendation could possibly be achieved by the release and analysis of individual data.

In the ESPN study, an exploratory analysis revealed subtype-dependent differences in overall survival. A previous large scale retrospective dataset in non-ccRCC suggested similar results [15]. The results of these studies suggest that a collective light microscopy-based trial eligibility of non-ccRCC subtypes is inappropriate. Multiple noncomparative studies suggest that non-ccRCC subtypes require an individual subtype and gene analysis-driven approach to augment therapeutic strategies in the future. Due to the small sample size, these findings are hypothesis generating, and multi-institutional cooperation would be required to conduct studies for selected subtypes. Interestingly, the exploratory analysis in ESPN showed that median OS was longer with both agents for patients with chromophobe RCC. In one patient with chromophobe RCC, a 58% decrease in tumor diameter with everolimus appeared to be associated with a TSC-2 mutation. Furthermore, in the ASPEN study a median PFS of 11.4 mo was reported for chromophobe RCC with everolimus versus 5.5 mo with sunitinib. The MET oncogene pathway in papillary RCC is another example of what could become a pathway-driven subtype-specific approach. Initially thought to be responsible in hereditary forms and to a lesser extent in sporadic papillary RCC, MET has recently been reported to be altered across both sporadic papillary types in a high percentage of 220 cases analyzed [16]. In a comprehensive analysis of non-ccRCC samples with next generation sequencing, a majority of papillary RCC had amplification, mutation or overexpression of MET [17] and even among type-2 papillary RCC phenotypically distinct subtypes have been described [18].

Foretinib, an oral broad kinase inhibitor targeting MET among other receptors, including VEGF, AXL, and TIE-2, was studied in a 74-patient phase 2 biomarker study, and it resulted in a median PFS of 9.3 mo [19]. An analysis of germline and somatic MET mutation was part of the study, which showed that the objective response rate for patients with germline or somatic MET mutation was 50% and 20%, respectively, versus only 8.8% in those without [19]. These results and the genomic studies suggest that patients with papillary RCC should be stratified according to their MET alteration status. Genomic analysis revealed further genes involved in other non-ccRCC subtypes as possible therapeutic targets, including gene sets that could be used to stratify patients in clinical trials [20].

3.5.5. Strengths and limitations of review

The strengths of the review are the systematic, prespecified, and transparent literature search about a topic in which a knowledge gap exits. All identified studies were RCTs with relatively low-to-moderate RoB. Two studies were sufficiently homogenous to allow meta-analysis. Limitations include the clinical and methodological heterogeneity of included studies in terms of study design, histological subtypes, and variants within the non-ccRCC group, and types and sequencing of treatment.

4. Conclusions

In conclusion, in the treatment of patients with metastatic non-ccRCC, the systematic review found numerically superior outcomes for sunitinib in comparison with everolimus in terms of OS and PFS, although the findings did not reach statistical significance. Although sunitinib was associated with more frequent Grade 3–4 adverse events, this finding was not statistically significant. Both agents have relatively modest effectiveness in non-ccRCC subtypes, and their relative benefits and adverse effects remain uncertain. Patients with non-ccRCC should be referred for clinical trials and management. To better account for the influence of subtype variabilities, an individual patient data meta-analysis involving all relevant trials of sunitinib versus everolimus in non-ccRCC is recommended.

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Appendix A. Supplementary data

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