Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2016-B-059 Cabozantinib

Datum: 07.06.2016

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Cabozantinib in Kombination mit Everolimus zur Behandlung des inoperablen, fortgeschrittenen oder metastasierten Nierenzellkarzinoms nach anti-VEGF Therapie	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Strahlentherapie (bei inoperablen Metastasen)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Axitinib – Beschluss über die Nutzenbewertung nach § 35a SGB V vom 21. März 2013
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche.*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** **(Text aus Fachinformation)**
Zu prüfendes Arzneimittel:	
Cabozantinib N.N. Cabometyx®	<u>Laut Positive Opinion vom 21.07.2016:</u> "Cabometyx is indicated for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy."
Everolimus L01XE10 Afinitor®	<u>Nierenzellkarzinom</u> Afinitor ist zur Behandlung von Patienten mit fortgeschrittenem Nierenzellkarzinom indiziert, bei denen es während oder nach einer gegen VEGF gerichteten Therapie zu einer Krankheitsprogression kommt.
Pazopanib L01XE11 Votrient®	Votrient ist angezeigt zur Erstlinien-Behandlung von erwachsenen Patienten mit fortgeschrittenem Nierenzellkarzinom und zur Behandlung von Patienten, die vorher eine Therapie ihrer fortgeschrittenen Erkrankung mit Zytokinen erhalten hatten.
Sorafenib L01XE05 Nexavar®	Nexavar ist angezeigt zur Behandlung von Patienten mit fortgeschrittenem Nierenzellkarzinom, bei denen eine vorherige Interferon-alpha- oder Interleukin-2-basierte Therapie versagt hat oder die für solch eine Therapie nicht geeignet sind.
Sunitinib L01XE04 SUTENT®	SUTENT wird bei Erwachsenen zur Behandlung fortgeschrittener/metastasierter Nierenzellkarzinome (mRCC) eingesetzt.
Axitinib L01XE17 Inlyta®	Inlyta ist angezeigt zur Behandlung des fortgeschrittenen Nierenzellkarzinoms (renal cell cancer, RCC) bei erwachsenen Patienten nach Versagen von vorangegangener Therapie mit Sunitinib oder einem Zytokin.
Nivolumab L01XC17 Opdivo®	OPDIVO ist als Monotherapie bei Erwachsenen zur Behandlung des fortgeschrittenen Nierenzellkarzinoms nach Vortherapie indiziert.
Interferon alfa-2a L03AB04 Roferon®-A	Roferon-A wird für die Behandlung der folgenden Erkrankungen angewendet: - Fortgeschrittenes Nierenzell-Karzinom.

Aldesleukin L03AC01 PROLEUKIN® S	Zur Behandlung des metastasierten Nierenzellkarzinoms. Risikofaktoren, die zu reduziertem Ansprechen und mittlerem Überleben führen, sind: - Ein reduzierter Allgemeinzustand von ECOG 1 oder mehr - Metastatischer Befall in mehr als einem Organ - Ein Intervall von weniger als 24 Monaten zwischen Primärdiagnose und Ansetzen der Proleukin-S-Therapie. Ansprechraten und mittlere Überlebenszeit werden mit zunehmender Anzahl vorhandener Risikofaktoren geringer. Patienten mit allen drei Risikofaktoren sollten nicht mit Proleukin S behandelt werden.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation fortgeschrittenes Nierenzellkarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 30.03.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw. Internetseiten folgender Organisationen gesucht: CCO, ESMO, NCCN, NCI. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 942 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 20 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Zur Behandlung von Patienten mit fortgeschrittenem Nierenzellkarzinom (RCC), die eine Vorbehandlung erhalten haben.

Berücksichtigte Wirkstoffe/Therapien:

Siehe Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Abkürzungen:

AE	Unerwünschte Ereignisse (Adverse Events)
Akdae	Arzneimittelkommission der deutschen Ärzteschaft
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
CCO	Cancer Care Ontario
CI	Konfidenzintervall (Confidence Interval)
CrI	Credibility Interval
DAHTA	Deutsche Agentur für Health Technology Assessment
DoR	Duration of response
DRKS	Deutsches Register Klinischer Studien
EBS	Evidence based series
ESMO	European Society for Medical Oncology
FKSI	Functional Assessment of Cancer Therapy Kidney Symptom Index questionnaire
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of recommendation
HR	Hazard Ratio
ICTRP	International Clinical Trials Registry Platform
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISRCTN	International Standard Randomised Controlled Trial Number
LoE	Level of evidence
mRCC	Metastiasiertes Nierenzellkarzinom (Metastatic Renal Cell Carcinoma)
mTOR	Mammalian target of rapamycin inhibitors
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence

ORR	Objective response rate
OS	Overall survival
PFS	Progression free survival
RCC	Nierenzellkarzinom (Renal Cell Carcinoma)
SIGN	Scottish Intercollegiate Guidelines Network
TKI	Tyrosine kinase inhibitors
TRIP	Turn Research into Practice Database
VEGF	Vascular endothelial growth factor
WBRT	Whole brain ratiotherapy
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

G-BA, 2013 [9]. Zusammenfassende Dokumentation über die Änderung der Arzneimittel-Richtlinie (AM-RL) Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Axitinib Stand: 10. September 2013 *siehe auch:* **IQWiG, 2012 [14].** Axitinib – Nutzenbewertung gemäß § 35a SGB V (IQWiG-Berichte – Nr. 149)	**Fazit:** Zugelassenes Anwendungsgebiet von Axitinib (Inlyta®) gemäß Fachinformation (Stand: September 2012): Inlyta® ist angezeigt zur Behandlung des fortgeschrittenen Nierenzellkarzinoms bei erwachsenen Patienten nach Versagen von vorangegangener Therapie mit Sunitinib oder einem Zytokin. Zweckmäßige Vergleichstherapie: a) Nach vorangegangener Therapie mit Sunitinib: Everolimus Wahrscheinlichkeit und Ausmaß des Zusatznutzens a) Nach vorangegangener Therapie mit Sunitinib: Ein Zusatznutzen von Axitinib nach vorangegangener Therapie mit Sunitinib gegenüber der zweckmäßigen Vergleichstherapie Everolimus ist **nicht belegt**.

Systematische Reviews

Ibrahim EM et al., 2013 [13]. Sunitinib adverse events in metastatic renal cell carcinoma: a meta-analysis	1. Fragestellung Sunitinib, a multi-targeted receptor tyrosine kinase inhibitor, has demonstrated survival benefit in patients with metastatic renal cell carcinoma (mRCC); however, significant adverse events (AEs) have been associated with its use. The significant variation in the reported incidences of AEs has prompted this meta-analysis to quantify the risk and explore associated predictors.
	2. Methodik Population: Patients at any age or gender with mRCC Intervention*:* Sunitinib (Hinweis: jede Linie) Komparator: Nicht definiert Endpunkt: AEs Suchzeitraum (Aktualität der Recherche): bis 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 Studien (darunter 9 einarmige und 3 randomisierte Studien) Zusätzlich wurde noch eine retrospektive Studie eingeschlossen, die 175 vorbehandelte Patienten einschloss mit den Endpunkten: Bluthochdruck und verminderte Auswurffraktion Qualitätsbewertung der Studien: The MINORS (Methodological Index for Non-Randomized Studies) tool was chosen for assessing the quality of the nonrandomized studies, whereas the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting criteria were used to assess the quality of randomized controlled trials. The authors discussed any significant discrepancy in the quality scores assigned to reach a consensus.
	3. Ergebnisdarstellung • The meta-analysis included 5,658 patients: 3,176 (66 %) patients had prior systemic therapy whereas the remaining 1,942 (34 %) patients received sunitinib in the first-line setting. • For any grade toxicity, skin rash, fatigue, diarrhea, and mucositis were the most frequently encountered events (81, 52, 45, and 33 %, respectively). Anemia, neutropenia, or thrombocytopenia of any grade occurred in more than one third of patients, although grades 3 or 4 were less common. • Any grade raised by liver enzymes or serum creatinine occurred in 40 and 44 % of patients, respectively.

	• The incidence of AEs was higher when sunitinib was used in pretreated versus naive patients; however, there was no significant difference between the two groups concerning the incidence of laboratory abnormalities.
	4. Fazit der Autoren: The present meta-analysis quantified sunitinib-associated AEs. The derived estimates would be similar to that to be expected from the use of sunitinib in community practice in unselected patients with metastatic renal cell carcinoma (mRCC).
Heng DY et al., 2014 [10]. Comparative Effectiveness of Second-Line Targeted Therapies for Metastatic Renal Cell Carcinoma: A Systematic Review and Meta-Analysis of Real-World Observational Studies	1. Fragestellung The optimal sequencing of targeted therapies for metastatic renal cell carcinoma (mRCC) is unknown. Observational studies with a variety of designs have reported differing results. The objective of this study is to systematically summarize and interpret the published real-world evidence comparing sequential treatment for mRCC.
	2. Methodik Population: Patients with mRCC Intervention/Komparator: observational studies comparing second-line mRCC treatment with mammalian target of rapamycin inhibitors (mTORi) versus vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKI) Endpunkte: Overall Survival (OS), Progression-free-survival (PFS) Suchzeitraum (Aktualität der Recherche): bis 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 Studien. Qualitätsbewertung der Studien: In order to evaluate the reliability of comparative evidence, a pre-planned assessment of study designs was conducted. Included studies were classified according to criteria derived from the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies. • First, we required studies to follow a retrospective cohort design that imposed inclusion criteria only up to the initiation of second-line therapy, and then followed all included patients as long as possible for outcomes. • As a second criterion, we required studies to report comparative outcomes that were adjusted for patients' characteristics prior to the initiation of second-line treatment. • Finally, we required studies to draw data from multiple treatment centers, as such studies are considered more representative and

generalizable than single-center studies

3. Ergebnisdarstellung

Among the 12 studies, 10 reported treatment effects on OS and 7 reported effects on PFS and were subsequently included in further analyses for OS and PFS, respectively. Studies reporting OS included a pooled total of 2,228 patients: 961 patients who received second-line mTORi and 1,267 patients who received second-line VEGF TKI. Studies reporting PFS included a pooled total of 1,926 patients: 916 patients who received second-line mTORi and 1,010 patients who received second-line VEGF TKI.

Study	Data Source	Inclusion Criteria	mTORi included	VEGF TKI included	Retrospective Cohort	Adjustment	Multicenter	N, mTORi	N, VEGF TKI	OS HR (95% CI)[a]	PFS HR (95% CI)[b]
Busch et al. 2011	Medical records from 2 centers in Germany	Progression on first-line VEGF TKI	Everolimus	Sunitinib and sorafenib	Y	Y[d]	Y	62	46	0.79 (0.43, 1.45)	0.86 (0.57–1.28)[d]
Chen et al. 2012	US claims data	Received sunitinib	Everolimus	Sorafenib	Y	Y	Y	117	65	1.03 (0.59, 1.79)	N/A
Heng et al. 2012[c]	International registry (Canada, United States, Singapore, and Denmark)[b]	Received first-line VEGF TKI	Everolimus and temsirolimus	Sunitinib and sorafenib	Y	Y[d]	Y	277	541	0.84 (0.67, 1.06)	1.18 (0.92–1.5)[d]
Wong et al. 2013	Nationwide chart review in the United States	Failed first-line VEGF TKI	Everolimus	Sorafenib	Y	Y	Y	233	123	0.65 (0.42, 0.99)	0.75 (0.53–1.07)
Park et al. 2012	Medical records from a single center in South Korea	Failed first-line VEGF TKI	Everolimus and temsirolimus	Sunitinib and sorafenib	Y	Y[d]	N	42	41	1.71 (0.86, 3.4)	1.03 (0.62–1.69)[d]
Gore et al. 2013	Multicenter, Australia, Brazil, Canada, Europe, United States	Received first-line sunitinib in a randomized trial	Everolimus, temsirolimus, Sirolimus and SGN-75	Sunitinib and sorafenib	Y	N	Y	42	171	1.05 (0.71, 1.54)	N/A
Harrison et al. 2012	Multicenter, United States	Patients alive since January 2007 and diagnosed between January 1, 2007, and February 7, 2011	Not specified	Not specified	N	N	Y	33	32	3.13 (0.96, 10.22)	N/A
Ruiz et al. 2013	Single-institution, Spain	Received at least 1 line of target therapy between 2007 and 2011	Everolimus and temsirolimus	Sunitinib, sorafenib, bevacizumab, pazopanib, axitinib[e], dovitinib	Y	N	N	19	34	1.10 (0.56, 2.17)	N/A
Busch et al. 2013	Medical records from 2 centers in Germany	Failure of first-line VEGF TKI	Everolimus and temsirolimus	Sunitinib and sorafenib	N	Y[d]	Y	41	62	0.86 (0.51, 1.44)	0.76 (0.43–1.35)[d]

Study	Data Source	Inclusion Criteria	mTORi included	VEGF TKI included	Retro spective Cohort	Adjust ment	Multi center	N, mTORi	N, VEGF TKI	OS HR (95% CI)[a]	PFS HR (95% CI)[b]
Iacovelli et al. 2013	Medical records from multiple centers in Italy	Patients consecu-tively trea-ted with 3 targeted therapies	Everolimus and temsirolimus	Sunitinib and sorafenib	N	Y	Y	95	152	2.59 (1.59, 4.22)	N/A
Elaidi et al. 2013	Medical records from 7 centers in Europe	Received VEGF TKI-VEGF TKI or VEGF TKI-mTORi	Everolimus and temsirolimus	Sunitinib, sorafenib, pazopa-nib, axitinib[e]	Y	Y	Y	123	118	N/A	1.56 (1.11–2.22)
Signorovitch et al. 2013	Chart review, multicenter, United States	Started second-line tar-geted therapy in 2010 or later	Everolimus and temsirolimus	Sunitinib, sorafenib, pazopa-nib, axitinib[e]	Y	Y	Y	138	79	N/A	0.74 (0.48, 1.15)

Pooled HRs and associated 95% confidence intervals (CIs) and P values were estimated under a random effects model.

<u>OS (basierend auf 10 Studien):</u>

- No significant difference in OS was identified between treatment sequences in this overall meta-analysis (HR=1.11, 95% CI 0.84–1.45, P=0.491), and, more importantly, the pooled effect estimate is difficult to interpret due to the significant heterogeneity.
- A meta-analysis including only the 4 adjusted, multicenter, retrospective cohort studies was also performed. These 4 studies included a total of 1,464 patients, constituting over half of the total number of patients in all 10 studies. 689 of these patients received mTORi (.75% everolimus) and 775 patients received VEGF TKI therapy (>60% sorafenib, no axitinib) in the secondline. There was no evidence of heterogeneity in the comparative effects estimates among these 4 studies (I^2=0%; P=0.608). In a meta-analysis of these four studies meeting reliability criteria, second-line mTORi was associated with significantly prolonged OS compared with VEGF TKI, corresponding to an 18% reduction in the hazard of death (HR=0.82, 95% CI 0.68 to 0.98, P=0.028).

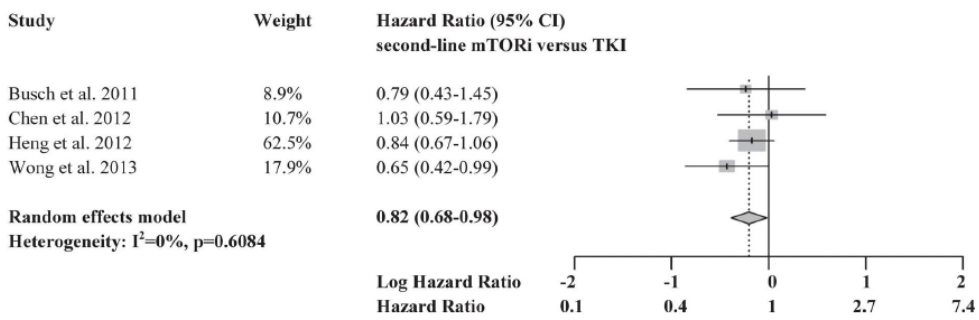


Fig. 4. Forest plots of 4 studies meeting all reliability criteria reporting comparative OS results.

4. Anmerkungen/Fazit der Autoren

It is notable that after focusing the meta-analysis on adjusted, multicenter, retrospective cohort studies, there was no evidence of heterogeneity in estimated second-line treatment effects on OS. This suggests that these four studies, although based on diverse data sources including a prospective multi-national registry, medical records from Germany, a retrospective chart review in the US and US claims data, are estimating the same underlying association between second-line treatment and OS. The pooled estimate from these studies showed a significant association between use of mTORi and prolonged OS compared with VEGF TKI in the second-line setting. The magnitude of the difference was clinically significant, representing an 18% decrease in the hazard of death associated with second-line mTORi.

This review and meta-analysis of observational studies carries important limitations. The foremost limitation is that the meta-analyses are based on nonrandomized treatment comparisons. The comparisons between drug classes may be confounded by differences in the types of patients treated with each class.

Potential confounding factors may include, for example, differences in age, metastatic burden, RCC histology, performance status, response to first VEGF TKI, lab values (e.g., neutrophil count, platelet count, corrected calcium level) or composite risk scores (e.g., MSKCC or Heng et al. criteria).

<u>Conclusions</u>

In this systematic review, real-world studies employed different designs and reported heterogeneous results comparing the effectiveness of second-line mTORi and VEGF TKI in the treatment of mRCC. Due to the high heterogeneity, it was not possible to draw a comparative conclusion from

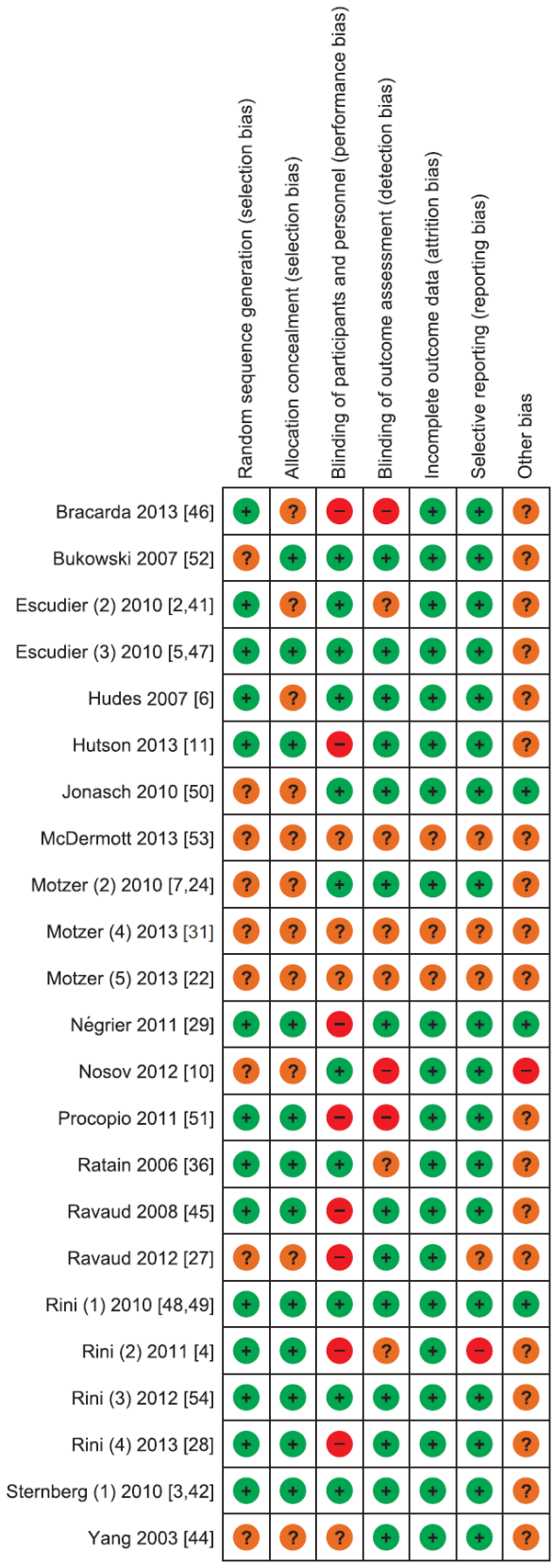
	the full set of identified studies. In a sub-analysis of studies with more reliable designs for comparative analysis (i.e., adjusted, multicenter, retrospective cohort studies), second-line use of mTORi was associated with significantly prolonged OS compared with secondline use of VEGF TKI in the treatment of mRCC. Real-world outcomes for axitinib were not available at the time of this analysis, and should be considered in future studies.
Albiges L et al., 2015 [2]. **EAU – European Association of Urology** A Systematic Review of Sequencing and Combinations of Systemic Therapy in Metastatic Renal Cancer	1. Fragestellung To systematically review relevant literature comparing the clinical effectiveness and harms of different sequencing and combinations of systemic targeted therapies for mRCC.
	2. Methodik Population: patients with metastatic renal cell carcinoma Intervention: combining or sequencing systemic targeted therapies Komparator: aktive Substanz oder Placebo Endpunkt: PFS, OS, harms of treatment Suchzeitraum (Aktualität der Recherche): 2000 to September 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 24 RCTs für qualitative Betrachtung, 4 für quantitative Auswertung. Qualitätsbewertung der Studien: Cochrane risk of bias tool
	3. Ergebnisdarstellung **Kurzzusammenfassung der Studien**

Table 1 – Retrieved phase 2 and 3 studies from systematic research in the cytokine-refractory setting, in the post–vascular endothelial growth factor inhibition setting, and in the third-line setting

Clinical trial	Design	*n*	PFS, mo	OS, mo
Cytokine pretreated				
Sorafenib vs placebo TARGET [2,41]	Phase 3	903	5.8 vs 2.8	17.8 vs 14.3 When censoring the crossover patients
Pazopanib vs placebo [3,42]	Phase 3	435 Prior cytokines: 46% (n = 202)	Overall population: 9.2 vs 4.2 Post cytokine: 7.4 vs 4.2	22.9 vs 20.5 Extensive crossover from placebo to pazopanib confounded final OS analysis
Axitinib vs sorafenib AXIS [4,43]	Phase 3	723 Prior cytokines: 35% (n = 251)	Overall population: 6.7 vs 4.7 Post cytokine: 12.2 vs 6.5	Overall population: 20.1 vs 19.9
Bevacizumab HD (10 mg/kg) vs bevacizumab LD (3 mg/kg) vs placebo [44]	Randomised phase 2	116 Post IL-2: 93%	4.8 vs 3.0 vs 2.5	NS
Lapatinib vs hormone [45] in mRCC that expresses EGFR and/or HER-2	Phase 3	416	15.3 vs 15.4	10.8 vs 9.9
VEGF inhibition refractory				
Everolimus vs placebo RECORD-1 [7,12,24]	Phase 3	Overall population: 416 Pure second-line setting after one TKI: 21% (n = 89) Following cytokine and one TKI: 53% (n = 219)	Overall population: 4.6 vs 1.8 Post one TKI: 5.2 vs 1.8 Post sunitinib: 4.6 vs 1.8	Overall population: 14.8 vs 14.4 Survival corrected for crossover was 1.9-fold longer with everolimus
Axitinib vs sorafenib AXIS [4,43]	Phase 3	723 Sunitinib pretreated: 54% (n = 389)	Overall population: 8.3 vs 5.7 Postsunitinib: 4.8 vs 3.4	Overall population: 20.1 vs 19.2
Temsirolimus vs sorafenib INTORSECT [11]	Phase 3	512	4.3 vs 3.9	12.3 vs 16.6
Sunitinib/Everolimus vs Everolimus/Sunitinib RECORD-3 [21]	Phase 3	471 51.6% and 53.7% of patients, respectively, received second line within the clinical trial	PFS1: 10.7 vs 7.9 Combined PFS 1 + 2: 25.8 vs 21.1	32 vs 22.4
Sorafenib/Sunitinib vs Sunitinib/Sorafenib SWITCH-I [12]	Phase 3	365 57% and 42% of patients, respectively, received second line within the clinical trial	PFS 1: NS HR: 1.19; p = 0.92 Combined PFS 1 + 2: NS HR: 1.01; p = 0.54	NS HR: 0.997; p = 0.49
Third line				
Everolimus vs placebo RECORD-1 [7,12,24]	Phase 3	Pure third line after two TKIs: 26% (n = 108)	4 vs 1.8	–
Dovitinib vs sorafenib GOLD [22]	Phase 3	570	3.7 vs 3.6	11.1 vs 11.0 Interim analysis

EGFR = epidermal growth factor receptor; HD = high dose; HER = human epidermal growth receptor; HR = hazard ratio; IL = interleukin; LD = low dose; mRCC = metastatic renal cell carcinoma; NS = not significant; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

Risk of Bias



Quantitative synthesis (metaanalysis) was only performed for studies where there was no appreciable clinical or methodological heterogeneity.

Cytokine pretreated patients

Sequencing targeted therapy as second-line treatment in cytokine pretreated patients has been assessed in randomised phase 2 (sunitinib) and large phase 3 RCTs for sorafenib, pazopanib, and axitinib. The average PFS in these reports was approximately 8 mo in cytokine-refractory patients. Several doses of temsirolimus have been evaluated in a

	4. Fazit der Autoren: Summarizing the available evidence, it can be concluded that both everolimus and axitinib are valid options after first-line VEGF/VEGFR inhibition failure. Sorafenib, in view of the recent OS results of the INTORSECT trial, might be considered as an alternative option. However, current PFS of second-line treatment is limited, with a median of 4–5 mo. 5. Hinweise durch FB Med RCTs hatten häufig inhomogen vorbehandelte Studienpopulationen, siehe Tabelle 1 (oben); Aussagen sind somit einem hohen Verzerrungsrisiko unterworfen
Dranitsaris G et al., 2013 [7]. Small molecule targeted therapies for the second-line treatment for metastatic renal cell carcinoma: a systematic review and indirect comparison of safety and efficacy	1. Fragestellung There are no randomized trials comparing the safety and efficacy of everolimus to axitinib in patients who are refractory to sunitinib. In the absence of a randomized trial, statistical methods can be used to indirectly evaluate two or more drugs. The advantage of using indirect statistical techniques to conduct comparative effectiveness evaluations is their utilization of the best available evidence to provide answers to questions that have not been addressed through a randomized trial. In this study, Bayesian mixed treatment comparison (MTC) models were developed to perform an indirect comparison on the safety and efficacy between the second- line small molecule targeted therapies that have been approved for patients with metastatic RCC.
	2. Methodik Population: metastatic RCC, second-line Intervention: sorafenib, axitinib, everolimus and pazopanib for the second-line treatment Komparator: k.A. Endpunkt: The primary efficacy outcomes were PFS evaluated by independent assessment and objective tumor RR. Response rate was defined as complete (CR) or partial response based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. grade III/IV diarrhea, fatigue, rash, hand–foot skin reaction and stomatitis ; adverse events leading to the permanent discontinuation of treatment Suchzeitraum (Aktualität der Recherche): 2005 to June 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 RCTs Qualitätsbewertung der Studien: Wurde nicht vorgenommen

Indirect statistical comparison

A Bayesian MTC model was fitted for each of the efficacy and toxicity outcomes using WinBUGs and R. Relative HR were estimated for PFS assuming an exponential survival model. The model estimates odds ratios (ORs) for tumor response and treatment discontinuation; relative rates are estimated for toxicities. As suggested by Cai et al. (2010), a Poisson likelihood was assumed in the case of toxicities to overcome the issue of small event rates.

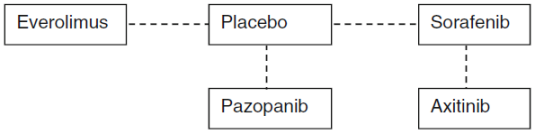


Fig. 1 Network diagram for RCC analysis

3. Ergebnisdarstellung

Table 1 Randomized trials evaluating oral therapies in second-line metastatic RCC

Citation	Line	Study arms	Num Pat
Escudier (2007, 2009)	2nd post-cytokines	So versus P	451, 452
Motzer (2008, 2012)	Post SU, So or cytokines	E versus P	272, 138
Sternberg (2010)	1st and 2nd post-cytokines	Pa versus P	290, 145
Rini (2011)	Post SU, B+IFN, or cytokines	A versus So	361, 362

Citation	Good to inter risk[a] (%)	Med age	Resp rate (%)	Med PFS (mo)	Med OS (mo)
Escudier (2007, 2009)	100, 99	58, 59	9.8 versus 1.8	5.5 versus 2.8[b]	17.8 versus 15.2[c]
Motzer (2008, 2012)	85, 85	61, 60	1 versus 0	4.9 versus 1.9[d]	NR versus 8.8[e]
Sternberg (2010)	94, 93	59, 60	30.3 versus 3.4	Overall: 9.2 versus 4.2	Overall: NR
			32 versus 4	1st line: 11.1 versus 2.8[f]	1st line: NR
			29 versus 3	2nd line: 7.4 versus 4.2[f]	2nd line: NR
Rini (2011)	65, 64	61, 61	19 versus 9	6.7 versus 4.7[g]	NR

PFS progression-free survival, *OS* overall survival, *Su* sunitinib, *INF* interferon alfa, *P* placebo, *So* sorafenib, *E* everolimus, *Pa* pazopanib, *A* axitinib, *B* bevacizumab, *T* temsirolimus.

[a] According to the Memorial Sloan-Kettering Cancer Center risk criteria (Motzer et al. 2004)

[b] HR 0.44; 95 % CI 0.35–0.55; $p < 0.001$

[c] HR 0.88; $p = 0.146$

[d] HR 0.30; 95 % CI 0.22–0.40, $p < 0.001$

[e] HR 0.83; 95 % CI, 0.50 to 1.37, $p = 0.23$

[f] First-line HR 0.40, 95 % CI 0.27–0.60, $p < 0.001$. Second-line HR 0.54, 95 % CI, 0.35–0.84, $p < 0.001$

[g] HR 0.66, $p < 0.001$

Only data reported in patients with prior cytokine exposure were used in the indirect comparison of PFS. However, toxicity data from the entire treated

	population were used in the indirect comparison of safety. Patients enrolled into each trial were comparable with respect to median age, gender and the enrollment of patients with a good performance status (primarily ECOG PS of 0 or 1). However, trial heterogeneity was noted in prognostic factors [as assessed by the Memorial Sloan-Kettering Cancer Center risk criteria] and prior first-line therapies. Indirect comparison of efficacy and safety between drugs The first clinical outcome evaluated in the indirect analysis was tumor RR, and it was expressed as an OR. An OR greater than one indicates improved tumor response. A CrI [credibility interval] around the point estimate is reported as a measure of uncertainty. A 95 % CrI above 1.0 gives a 95 % probability of improved tumor response. The findings revealed that pazopanib, axitinib and sorafenib were superior to placebo in terms of tumor response. In addition, axitinib was also superior to sorafenib. Patients treated with axitinib were twice as likely to achieve a tumor response compared to similar patients receiving sorafenib (OR 2.3; 95 % CrI 1.45–3.73). None of the other interdrug comparisons indicated significant differences between the second-line small molecule targeted therapies. The second clinical endpoint evaluated in the network meta-analysis was the hazard ratio (HR) for PFS. A hazard in this case indicates the instantaneous risk of disease progression. A HR of less than one therefore indicates an improved PFS of one agent evaluated against a comparator. A 95 % CrI below one allows for 95 % certainty for an improvement in PFS. All four small molecules were superior to placebo with respect to PFS. The indirect comparison suggested a similar PFS with everolimus, pazopanib and sorafenib. In contrast, axitinib was associated with a superior PFS when compared to pazopanib and sorafenib. No statistically significant difference was found between axitinib and everolimus. Given the comparable clinical outcomes with at least three of the four drugs in the second-line setting, medical decision making should be guided by which agents were used in the first-line setting, patient comorbidities and the risk of grade III/IV DLT. Everolimus and pazopanib were both associated with a higher risk of treatment discontinuations due to adverse events relative to placebo. Indirect estimates indicated that patients being treated with pazopanib or everolimus as an alternative to axitinib have an increased risk of discontinuation caused by adverse events. The data also suggest a

reduced risk of treatment discontinuation with sorafenib compared to pazopanib. However, the OR suggesting a reduced risk of sorafenib compared to everolimus did not reach statistical significance.

Comparison	Outcome (95 % CrI)	Significant improvement[c]
OR for tumor response[a]		
Everolimus versus placebo	3.12 (0.30–56.0)	Inconclusive
Everolimus versus axitinib	0.24 (0.02–5.0)	Inconclusive
Everolimus versus pazopanib	0.28 (0.02–6.8)	Inconclusive
Everolimus versus sorafenib	0.56 (0.05–11.0)	Inconclusive
Pazopanib versus placebo	11.3 (3.2–50)	Yes, pazopanib better
Pazopanib versus axitinib	0.87 (0.18–5.0)	Inconclusive
Pazopanib versus sorafenib	2.0 (0.46–10.7)	Inconclusive
Axitinib versus placebo	12.9 (5.5–32.3)	Yes, axitinib better
Axitinib versus sorafenib	2.3 (1.45–3.73)	Yes, axitinib better
Sorafenib versus placebo	5.6 (2.76–12.3)	Yes, sorafenib better
HR for PFS[b]		
Everolimus versus placebo	0.48 (0.36–0.64)	Yes, everolimus better
Everolimus versus axitinib	1.32 (0.88–2.0)	Inconclusive
Everolimus versus pazopanib	0.84 (0.56–1.28)	Inconclusive
Everolimus versus sorafenib	0.93 (0.66–1.32)	Inconclusive
Pazopanib versus placebo	0.56 (0.42–0.75)	Yes, pazopanib better
Pazopanib versus axitinib	1.57 (1.05–2.36)	No, axitinib better
Pazopanib versus sorafenib	1.10 (0.78–1.56)	Inconclusive
Axitinib versus placebo	0.36 (0.27–0.48)	Yes, axitinib better
Axitinib versus sorafenib	0.70 (0.57–0.87)	Yes, axitinib better
Sorafenib versus placebo	0.51 (0.42–0.62)	Yes, sorafenib better

Table 4 Summary of indirect statistical comparisons of toxicity outcomes using a Bayesian mixed treatment comparison model

Comparison	Outcome (95 % CrI)	Significant incremental risk[b]
OR for drug discontinuations[a]		
Everolimus versus placebo	3.29 (1.29 to 10)	Yes, with everolimus
Everolimus versus axitinib	4.0 (1.2 to 14.5)	Yes, with everolimus
Everolimus versus pazopanib	0.66 (0.16 to 2.71)	Inconclusive
Everolimus versus sorafenib	2.57 (0.91 to 8.26)	Inconclusive
Pazopanib versus placebo	5.0 (2.02 to 14.9)	Yes, with pazopanib
Pazopanib versus axitinib	6.07 (1.88 to 22.4)	Yes, with pazopanib
Pazopanib versus sorafenib	3.90 (1.41 to 12.6)	Yes, with pazopanib
Axitinib versus placebo	0.82 (0.40 to 1.70)	Inconclusive
Axitinib versus sorafenib	0.64 (0.36 to 1.12)	Inconclusive
Sorafenib versus placebo	1.28 (0.81 to 2.04)	Inconclusive

4. Anmerkungen/Fazit der Autoren

The findings of this indirect analysis of prospective randomized trials suggest that everolimus, sorafenib, axitinib and pazopanib are all able to induce tumor shrinkage and provide patients with a clinically meaningful PFS benefit. Keeping in mind caveats associated with cross-trial statistical

	comparisons, our findings also suggest a superior PFS benefit associated with axitinib relative to pazopanib and sorafenib. However, this comes at cost of a higher risk of fatigue and to a lesser extent stomatitis. Given its distinct mechanism of action and differing toxicity profile, everolimus is an effective option after an anti-VEGFR progression.
Iacovelli R et al., 2016 [12]. Is there still a role for sorafenib in metastatic renal cell carcinoma? A systematic review and meta-analysis of the effectiveness of sorafenib over other targeted agents *Siehe auch* **Kang S et al., 2015 [15].** Efficacy and Safety of Selective Vascular Endothelial Growth Factor Receptor	1. Fragestellung to investigate if there is still a role for sorafenib in mRCC in the era of new tyrosine kinase inhibitors.
	2. Methodik Population: mRCC in first- or subsequent lines of therapy (i.e., second and third) Intervention: targeted agents Komparator: sorafenib Endpunkt: OS and PFS Suchzeitraum (Aktualität der Recherche): November 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 RCTs. Qualitätsbewertung der Studien: Study quality was assessed using the Jadad seven-item scalet hat included randomization, double blinding, and withdrawals. The final score was reported to be between 0 and 5
	3. Ergebnisdarstellung **Table 1** Main characteristics of the included study.

Study	Phase	Pts Exp./Ctr.	Line	Clear cell Comp. (%)	Therapy		MSKCC Good Prognosis (%)	MSKCC Interm. Prognosis (%)	MSKCC Poor Prognosis (%)	Median treatment duration (months) Exp./Ctr.
					Experim.	Control				
GOLD	3	284/286	3	100	Dovitinib	Sorafenib	20/21	58/57	22/23	3.7
TIVO-1	3	260/257	1	100	Tivozanib	Sorafenib	27/34	67/62	7/4	12.0/9.5
AGILE	3	192/96	1	100	Axitinib	Sorafenib	49/55	44/42	4/2	12.4/10.1
AXIS	3	361/362	2	100	Axitinib	Sorafenib	28/28	37/36	33/33	6.4/5.0
SWITCH	3	183/182	1	87	Sunitinib	Sorafenib	44/39	51/55	1/1	11.0/9.4
INTORSECT	3	259/253	2	82	Temsirolimus	Sorafenib	19/17	69/70	12/13	4.4/3.6
CROSS-J-RCC	2	57/63	1	100	Sunitinib	Sorafenib	NA	NA	NA	NAf

Inhibitors Compared with Sorafenib for Metastatic Renal Cell Carcinoma: a Meta-analysis of Randomised Controlled Trials	

Study	ORR		PFS		OS		Jadad score
	Exp. (%)	Ctr. (%)	HR	95%CI	HR	95% CI	
GOLD	4%	4%	0.86	0.72–1.04	0.96	0.75–1.22	3
TIVO-1	33%	23%	0.77	0.64–0.93	1.25	0.95–1.62	3
AGILE	32%	15%	0.76	0.56–1.05	1.00	0.73–1.36	3
AXIS	19%	9%	0.67	0.54–0.81	0.97	0.80–1.18	3
SWITCH	29%	31%	0.84	0.68–1.04	1.00	0.77–1.30	3
INTORSECT	8%	8%	0.87	0.71–1.07	1.31	1.05–1.63	3
CROSS-J-RCC	NA	NA	0.68	0.43–1.08	NA	NA	NA

Abbreviations: CI = confidence interval; Comp = component; Ctr = control arm; Exp = experimental arm; Interm = intermediate; HR = hazard ratio; mos = months; MSKCC = Memorial Sloan Kettering Cancer Centre Prognostic classification; NA = not applicable; Pbo = placebo; PFS = progression free survival; Pts = patients.

Es werden im Folgenden nur die Ergebnisse für die Zweit- und Drittlinie dargestellt.

When substantial heterogeneity was not observed, the pooled estimate calculated based on the fixed-effects model was reported using the inverse variance method. Statistical heterogeneity between the trials included in the meta-analysis was assessed using the Chi-squared test, and inconsistency was quantified with the I2statistic (100% × [Q − df)/Q]). The assumption of homogeneity was considered to be invalid for p values less than 0.1.

PFS

- When the analysis was limited to patients treated with second- or third-line therapy, other TAs were able to reduce the risk of progression compared to sorafenib by 22% (random effect; HR = 0.78; 95% CI, 0.65–0.95; p = 0.01).This effect remained significant when the analysis was limited to patients enrolled in the AXIS and INTORSECT trials and previously treated with sunitinib (HR = 0.75; 95%CI, 0.57–0.99; p = 0.04).
- MSKCC in a good prognostic group: second-line treatment (HR = 0.58; 95% CI, 0.42–0.79; p < 0.001)
- MSKCC in the intermediate prognostic group: second-line therapy (HR = 0.89; 95%CI, 0.73–1.07; p = 0.21)

OS

When the analysis was limited to patients treated with second- or third-line therapy, other TAs were unable to reduce the risk of death compared to sorafenib (random effect, HR = 1.09; 95% CI, 0.87–1.38; p = 0.45). A lack of benefit in terms of other TAs was also present if the analysis was limited to patients previously treated with sunitinib enrolled in the AXIS and

	INTORSECT trials (random effect, HR = 1.15; 95% CI, 0.84–1.56;p = 0.39). **ORR** in the 1805 evaluable patients given second-line treatment, significant difference was found in favor of other TAs compared to sorafenib (random effect, RR = 1.13; 95% CI, 1.24–1.76; p < 0.001)
	4. Anmerkungen/Fazit der Autoren **Iacovelli et al.** Finally, this study demonstrates that other TAs only increased PFS, and not OS, when compared to sorafenib. Moreover, no significant difference with other TAs was found in terms of PFS when sorafenib was used as second-line treatment in patients with an intermediate prognosis. Based on these results, sorafenib might retain a role in the treatment of mRCC, even if its position in the clinical sequence should take into consideration the recent evidence favoring the use of PD1/PD-L1 and new VEGFR/MET inhibitors. Given the results of this analysis, sorafenib remains an on-detrimental option for subsequent lines of therapy. **Kang et al.** The selective VEGFR inhibitors showed statistically significant improved PFS and ORR, although overall survival did not differ compared with sorafenib. The lack of improved overall survival is difficult to interpret, as the lack of demonstrable improvement may be related to diluted effects of treatment as patients switched to variable therapies after the analysed trials, or a true lack of difference due to an underlying biological mechanism such as an initial response but eventual drug resistance or incomplete cytotoxicity. In conclusion, the use of selective VEGFR-targeted agents compared with sorafenib shows significant improvement in PFS and ORR. When considering the drugs axitinib and tivozanib, there is also significant improvement in DAE compared with sorafenib. Although these strengths are considered in balance with differences in side-effect profile and lack of demonstrable improvement in overall survival, the benefits support the value of these newer drugs and at the level of individual patients may aid in the selection of a sequence of therapeutic agents for metastatic RCC. 5. Hinweise durch FB Med In Kang et al. wurden die Studien GOLD, TIVO1, AGILE und AXIS eingeschlossen. Die Ergebnisse entsprechen quantitativ den Ergebnissen

	der Studie von Iacovelli et al.
Poggiani C et al., 2012 [20]. Axitinib for the second-line treatment of metastatic renal cell carcinoma (mRCC) *<u>siehe auch:</u>* **CADTH, 2013 [5].** Pan-Canadian Oncology Drug Review, Final Clinical Guidance Report: Axitinib (Inlyta) for metastatic Renal Cell Carcinoma Bewertung identischer Untersuchung: AXIS Studie	1. Fragestellung HTA des Ludwig Boltzmann Instituts (LBI) zur Bewertung von Axitinib for the second-line treatment of patients with advanced renal cell carcinoma (RCC).
	2. Methodik Population: patients with advanced renal cell carcinoma Intervention: Axitinib (AXIS Studie) Komparator: Sorafenib (AXIS Studie) Endpunkte: PFS, OS, ORR, DoR, TTD, Functional Assessment of Cancer Therapy Kidney Symptom Index questionnaire (FKSI), FKSI–Disease-Related Symptoms Suchzeitraum (Aktualität der Recherche): bis 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): Only randomized clinical trials which tested axitinib in the indication of interest (i.e. second-line therapy in patients with advanced RCC) were included in the evaluation of <u>efficacy</u> → AXIS Trial For <u>safety</u> evaluation two further single-arm phase II trials were included. Qualitätsbewertung der Studien: Allgemein nach dem GRADE Ansatz (zu entnehmen aus dem allgemeinen LBI Methodenpapier)
	3. Ergebnisdarstellung In der Studie → Previous systemic therapy with: Sunitinib: I 54% vs C 54% Cytokines: I 35% vs C 35% Bevacizumab: I 8% vs C 8% Temsirolimus: I 3% vs C 3% **PFS**: Major efficacy result of the pivotal AXIS trial is the statistically significant increase in median PFS of 2 months in the axitinib treated group compared to the control group (HR 0.665; 95% CI: 0.544 to 0.182; p<0.0001). <u>Subgroup analysis</u> of median PFS according to previous treatment shows that the increase in PFS is even higher in patients pre-treated with cytokines (+5.6 months) and temsirolimus (+4.8 months) compared to pre-treatment with the VEGFR targeting agents sunitinib (+1.4 months) or bevacizumab (-0.5 months). Comparing the control and intervention group,

	the increase in median PFS was statistically significant in cytokine and sunitinib pretreated patients, not in bevacizumab or temsirolimus, which might be due to the small number of included patients within the subgroups. The objective response rate was higher in the axitinib group (19%) than in the sorafenib group (9%) and the median duration of response differed by 0.4 months between these two groups. **OS**: The different post-progression treatment regimens make it difficult to measure the effect of axitinib on overall survival (OS) compared to sorafenib as the subsequent active therapy cannot yet be statistically controlled and will influence OS to an extent that is difficult to quantify [18]. In December 2011 Pfizer presented the final OS data to the Oncologic Drugs Advisory Committee, which did not demonstrate superiority of axitinib over sorafenib (HR 0.969, 95% CI 0.800 to 1.174; p=0.376) with a median OS of 20.1 and 19.2 months in the axitinib and sorafenib groups, respectively. **QoL**: The aspect of quality of life (QoL) was quantified using a composite endpoint consisting of time to death, disease progression, or worsening of symptoms. The latter was measured with the Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI) and the FKSI Disease-Related Symptoms (FKSI-DRS). Measurement of time to deterioration with both instruments lead to a risk reduction in the axitinib group compared to the sorafenib group of 17% and 16% with the FKSI-15 and FKSI-DRS questionnaire, respectively. **AE**: Within the AXIS trial, main adverse events (AEs) with axitinib vs. sorafenib were diarrhoea (55% vs. 53%); hypertension (40% vs. 29%); fatigue (39% vs. 32%); nausea (32 vs. 22%); dysphonia (31% vs. 14%); palmar-plantar erythrodysaesthesia (27% vs. 51%); vomiting (24% vs. 17%); asthenia (21% vs. 14%); hypothyroidism (19% vs. 8%); stomatitis (15% vs. 12%). Discontinuations due to AEs were 22 (6%) and 33 (9%) with axitinib and sorafenib, respectively and discontinuations due to treatment–related AEs were twice as frequent in the sorafenib group than in the axitinib group (I4% vs C 8%). No treatment-related deaths were observed in the axitinib group but two patients died in the sorafenib group. <u>Ergebnisse weiterer Studien zur Sicherheit (basierend auf → 2 single-arm, open-label phase II trials assessing the safety and efficacy of</u>

	axitinib in 114 pre-treated patients): Generally the most frequent reported AEs in single-agent axitinib trials are hypertension, fatigue and gastrointestinal toxicities. In sorafenib-pretreated patients the most common grade 3-4 AEs were fatigue, hypertension and handnofoot syndrome (each 16.1%), lymphopenia (16.4%) dyspnoea (12.9%), diarrhoea (14.5%) and abdominal pain (11.3%).
	4. Anmerkungen/Fazit der Autoren To sum up, the AXIS trial reached its goal to significantly improve median PFS with axitinib by 2 months compared to sorafenib; difference in median OS was not significant. Sub-group analyses indicate that the treatment effect of both VEGFR targeting agents, axitinib and sorafenib, was less pronounced in the sub-group of patients that failed prior TKI therapy with sunitinib. Thus, the question remains whether axitinib should be recommended for the treatment in patients pre-treated with a TKI targeting VEGFR and how the effectiveness and AE profiles compares to everolimus, the current standard of care in second-line treatment of mRCC after failure of VEGFR targeting TKIs.

Leitlinien

Leitlinienprogramm Onkologie, 2015 [16]. S3-Leitlinie Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms	Fragestellung: Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms
	Grundlage der Leitlinie **Methodisches Vorgehen:** • Für die Erstellung der Leitlinie wurden zunächst durch die Leitliniengruppe prioritäre Fragestellungen definiert, relevante Fragestellungen gesammelt und beim Kick-off-Treffen der Leitlinien-gruppe am 29.10.2012 konkretisiert und konsentiert. • Leitlinienadaption: Die Suche nach publizierten Leitlinien zu Diagnostik und Therapie des Nierenzellkarzinoms wurde im August 2012 durchgeführt und mittels DELBI Auswahl getroffen • Diagnostik, direkter Vergleich systemischer Therapien wurde durch das Department für Evidenzbasierte Medizin und Klinische Epidemiologie der Donau-Universität Krems durchgeführt und Literaturstellen ausgewählt und mittels GRADE-Methodik bewertet • 3 Konsensuskonferenzen mit TED-Abstimmung, finale schriftliche Abstimmung • Suchstrategie veröffentlicht • Evidenztabellen einsehbar **Literaturrecherche:** Ausgangsrecherche im Januar 2013, Systematische Aktualisierungsrecherche mit Pubmed für den Zeitraum von Januar 2013 bis Januar 2014, durchgeführt am 26.01.2014 Empfehlungen sind mit Literatur verknüpft LoE: Verwendung von System des Scottish Intercollegiate Guidelines Network (SIGN)

Tabelle 3: Schema der Evidenzgraduierung nach SIGN

Grad	Beschreibung
1++	Qualitativ hochwertige Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias)
1+	Gut durchgeführte Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit geringem Risiko systematischer Fehler (Bias)
1-	Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit hohem Risiko systematischer Fehler (Bias)
2++	Qualitativ hochwertige systematische Übersichten von Fall-Kontroll- oder Kohortenstudien oder Qualitativ hochwertige Fall-Kontroll- oder Kohortenstudien mit sehr niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und hoher Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2+	Gut durchgeführte Fall-Kontroll-Studien oder Kohortenstudien mit niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und moderater Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2-	Fall-Kontroll-Studien oder Kohortenstudien mit einem hohen Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und signifikantem Risiko, dass die Beziehung nicht ursächlich ist
3	Nicht-analytische Studien, z.B. Fallberichte, Fallserien
4	Expertenmeinung

GoR

Tabelle 4: Schema der Empfehlungsgraduierung

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll/soll nicht
B	Empfehlung	sollte/sollte nicht
0	Empfehlung offen	kann /kann verzichtet werden

Tabelle 5: Konsensusstärke

Konsenstärke	Prozentuale Zustimmung
Starker Konsens	> 95% der Stimmberechtigten
Konsens	> 75-95% der Stimmberechtigten
Mehrheitliche Zustimmung	≥ 50-75% der Stimmberechtigten
Dissens	< 50% der Stimmberechtigten

2.2.3. Statements

Als Statements werden Darlegungen oder Erläuterungen von spezifischen Sachverhalten oder Fragestellungen ohne unmittelbare Handlungsaufforderung bezeichnet. Sie werden entsprechend der Vorgehensweise bei den Empfehlungen im Rahmen eines formalen Konsensusverfahrens verabschiedet und können entweder auf

	Studienergebnissen oder auf Expertenmeinungen beruhen. 2.2.4. Expertenkonsens (EK) Statements/Empfehlungen, für die eine Bearbeitung auf der Grundlage von Experten-konsens (es erfolgt keine systematische Recherche) der Leitliniengruppe beschlossen wurde, sind als „Expertenkonsens“ ausgewiesen. Für die Graduierung der Empfehlun-gen die auf Expertenkonsens basieren, werden keine Empfehlungsstärken mittels Buchstaben verwendet. Die S3-Leitlinie ist bis zur nächsten Aktualisierung gültig, die Gültigkeitsdauer wird auf 3 Jahre geschätzt.
	Empfehlungen Beim metastasierten klarzelligen Nierenzellkarzinom soll eine alleinige Zytokintherapie basierend auf subkutanem IL-2 und/oder IFN nicht durchgeführt werden. (Empfehlungsgrad A, Level of Evidence 2++, starker Konsens) Evidenzbasis: Motzer, R.J., et al., Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med, 2007. 356(2): p. 115-24. PubMed: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17215529 286. Hudes, G., et al., Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med, 2007. 356(22): p. 2271-81. 287. Escudier, B., et al., Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet, 2007. 370(9605): p. 2103-11. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18156031 288. Rini, B.I., et al., Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol, 2008. 26(33): p. 5422-8. In der Zweitlinientherapie nach Sunitinib oder Zytokinen soll Axitinib verwendet werden. Für Axitinib nach Bevacizumab, Pazopanib oder Temsirolimus liegen keine ausreichenden Daten vor. *(Empfehlungsgrad A, Level of Evidence 1+, Konsens)* Evidenzbasis: 320. Motzer, R.J., et al., Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol, 2013. 14(6): p. 552-62. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/23598172 Nur nach Versagen von mindestens einem VEGF-Inhibitor soll Everolimus eingesetzt werden. *(Empfehlungsgrad A, Level of Evidence 1+, Konsens)*

Evidenzbasis:
323. Motzer, R.J., et al., Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet, 2008. 372(9637): p. 449-56. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18653228

Nach Versagen eines mTOR-Inhibitors kann die Folgetherapie mittels eines Tyrosin-kinaseinhibitors (TKI) erfolgen. *(Empfehlungsgrad 0, Level of Evidence 2, Konsens)*

Evidenzbasis:
Motzer, R.J., et al., Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: an open-label, randomised phase 3 trial. Lancet Oncol, 2014. 15(3): p. 286-96.

Tabelle 11: Systemtherapieoptionen gemäß Vortherapie in der Zweitlinientherapie

Therapielinie	Vortherapie	Standard	Option
Zweitlinie	nach Zytokinen	Axitinib	Pazopanib Sorafenib
	nach VEGF-Versagen	Everolimus	
	nach Sunitinib	Axitinib Everolimus	
	nach Temsirolimus	Axitinib Pazopanib Sorafenib Sunitinib	

Hintergrund:

Mit der Entwicklung der zielgerichteten Therapien ist die Zytokintherapie zunehmend aus der Klinik verschwunden. Die verschiedenen neuen Substanzen weisen in den entsprechenden Zulassungsstudien jeweils eine signifikante Verbesserung des progressionsfreien Überlebens gegenüber IFN auf. Kontemporäre Phase-III-Studien bestätigen mit einem Gesamtüberleben von ca. 29 Monaten (Immuntherapie: 13,3 Monate, siehe oben) die Relevanz dieser neuen Substanzen in der Erstlinienbehandlung.

Nach einer Vortherapie mit Sunitinib stehen Axitinib und Everolimus für die Folgetherapie zur Verfügung. Auch hier gilt, dass aufgrund eines fehlenden direkten Vergleichs keine Priorisierung der Therapiewahl erfolgen kann, sodass beide Substanzen als Optionen in der Folgetherapie zugelassen sind. Da die Zulassungsstudie für Everolimus mehr als eine Vortherapie erlaubte, wird die Substanz generell nach Versagen der VEGF-Inhibition empfohlen, wohingegen der Einsatz von Axitinib auf die Zweitlinie beschränkt bleibt. Beide Substanzen stellen

	damit probate Optionen für vorbehandelte Patienten dar. Einschränkungen für den Einsatz ergeben sich aus der Zulassung. So ist Axitinib lediglich nach einer Vorbehandlung mit Sunitinib oder Zytokinen zugelassen. Everolimus hingegen ist nur auf eine Vorbehandlung mit einem VEGF-Inhibitor beschränkt. Das signifikant verbesserte progressionsfreie Überleben (progression-free survival, PFS) für Axitinib vs. Sorafenib in der AXIS-Studie (6,7 vs. 4,7 Monate; HR 0,665) konnte zwar keine Verbesserung für das Gesamtüberleben erzielen (20,1 vs. 19,2 Monate; HR 0,97), die Ergebnisse sind allerdings konsistent mit einer Netzwerkanalyse (verbessertes PFS: HR 0,67) und unterstützen damit die Empfehlung für Axitinib in dieser Therapiesituation Die Qualität der Evidenz, dass Axitinib und Sorafenib ein ähnliches Gesamtüberleben erzielen, ist moderat. Die Qualität der Evidenz, dass Axitinib zu einem längeren PFS bei ähnlicher Lebensqualität führt, ist niedrig. Mit der GOLD-Studie stehen mittlerweile auch Daten zur Drittlinientherapie zur Verfügung. Die Studie testete Dovitinib und Sorafenib nach Versagen eines mTOR- und eines VEGFR-Inhibitors. Das PFS war mit 3,7 und 3,6 Monaten ähnlich, ein Unterschied im Gesamtüberleben konnte nicht generiert werden (11,1 vs. 11,0 Monate) [324]. Diese Daten stützen die Fortsetzung der Tumortherapie mit dem Einsatz eines Tyrosinkinaseinhibitors in der Drittlinie, da die Daten zur fortgesetzten Therapie effektiver erscheinen als in der Placebo-Kontrolle der RECORD-1-Studie (nach VEGF-Versagen: 1,9 Monate) [323]. Evidenzbasis: 323. Motzer, R.J., et al., Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet, 2008. 372(9637): p. 449-56. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18653228 324. Motzer, R.J., et al., Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: an open-label, randomised phase 3 trial. Lancet Oncol, 2014. 15(3): p. 286-96. 325. Motzer, R.J., et al. Record-3: Phase II randomized trial comparing sequential first-line everolimus (EVE) and second-line sunitinib (SUN) versus first-line SUN and second-line EVE in patients with metastatic renal cell carcinoma (mRCC). in ASCO Annual Meeting Proceedings. 2013.
Ljungberg B et al., 2015 [17]. Guidelines on Renal Cell	Fragestellung: The European Association of Urology (EAU) Renal Cell Cancer (RCC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of RCC.

<table>
<tr>
<td>Carcinoma</td>
<td>
Methodik

Grundlage der Leitlinie

– Update of 2010 version
– Development by multidisciplinary panel
• Systematic Review on
  • […]
  • systemic therapy for metastatic RCC (b)
  • […]
    ○ Search up to the end of November 2013
    ○ Datenbanken: Cochrane Database of Systematic Reviews, the Cochrane Library of Controlled Clinical Trials, Medline and Embase
    ○ RCTs or quasi-RCTs für (b)
    ○ Risk of bias assessment using Cochrane Risk of Bias Tool
– remaining sections updated using a traditional narrative review strategy

LoE modified from Oxford Centre for Evidence-based Medicine

<table>
<tr><th>Level</th><th>Type of evidence</th></tr>
<tr><td>1a</td><td>Evidence obtained from meta-analysis of randomised trials.</td></tr>
<tr><td>1b</td><td>Evidence obtained from at least one randomised trial.</td></tr>
<tr><td>2a</td><td>Evidence obtained from one well-designed controlled study without randomization.</td></tr>
<tr><td>2b</td><td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td></tr>
<tr><td>3</td><td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.</td></tr>
<tr><td>4</td><td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.</td></tr>
</table>

GoR modified from Oxford Centre for Evidence-based Medicine

<table>
<tr><th>Grade</th><th>Nature of recommendations</th></tr>
<tr><td>A</td><td>Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.</td></tr>
<tr><td>B</td><td>Based on well-conducted clinical studies, but without randomised clinical trials.</td></tr>
<tr><td>C</td><td>Made despite the absence of directly applicable clinical studies of good quality.</td></tr>
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<td></td>
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Systemic therapy for advanced/metastatic RCC

Targeted therapies

<u>Recommendations</u>
Systemic therapy for mRCC should be based on targeted agents. (LoE: A)

Axitinib is recommended as second-line treatment for mRCC. (LoE: A)

Everolimus is recommended for ccRCC patients who have failed VEGF-
</td>
</tr>
</table>

targeted therapy. (LoE: A)

Sequencing of targeted agents is recommended. (LoE: A)

Evidence
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Tyrosine kinase inhibitors

Sorafenib

Sorafenib is an oral multikinase inhibitor. A trial compared sorafenib and placebo after failure of prior systemic immunotherapy or in patients unfit for immunotherapy. Sorafenib improved PFS (HR: 0.44; 95% CI: 0.35-

	0.55; p < 0.01). OS improved in patients who crossed over from placebo to sorafenib. A number of studies have used sorafenib as the control arm in sunitinib-refractory disease versus axitinib, dovitinib and temsirolimus. None showed superior survival compared to sorafenib. Sunitinib Sunitinib is an oral tyrosine kinase (TK) inhibitor and has antitumour and anti-angiogenic activity. Sunitinib as second-line monotherapy in patients with mRCC demonstrated a partial response in 34-40% and stable disease > 3 months in 27-29% of patients. [Anmerkung FB-Med: Vorbehandlung mit Zytokinen siehe Ref. 343] Axitinib Axitinib is an oral selective second-generation inhibitor of VEGFR-1, -2, and -3. Axitinib was first evaluated as second-line treatment. In the AXIS trial (axitinib versus sorafenib in patients with previously failed cytokine treatment or targeted agents), the sample size calculation was based on a 40% improvement in median PFS from 5-7 months in patients receiving axitinib. The overall median PFS was greater for axitinib than sorafenib. The difference in PFS was greatest in patients in whom cytokine treatment had failed. For those in whom sunitinib had failed, axitinib was associated with a greater PFS than sorafenib (4.8 vs. 3.4 months). Axitinib showed > grade 3 diarrhoea in 11%, hypertension in 16%, and fatigue in 11%. Across all grades, nausea was recorded in 32%, vomiting in 24%, and asthenia in 21%. OS was a secondary end-point of the trial in which crossover was not permitted. Final analysis of OS showed no significant differences between the groups in second-line treatment. **mTOR inhibitors** Everolimus: Everolimus is an oral mTOR inhibitor, which is established in the treatment of VEGF-refractory disease. The RECORD-1 study compared everolimus + best supportive care (BSC) vs. placebo + BSC in patients with previously failed anti-VEGFR treatment (or previously intolerant of VEGF targeted therapy). The initial data showed a median PFS of 4.0 months v.s. 1.9 months for everolimus and placebo, respectively. This was extended to 4.9 months in the final analysis HR=0.33. Subset analysis of PFS for patients receiving only 1 previous VEFG TKI was 5.4 months. This included some patients who were intolerant rather than progressed on therapy (PFS also 5.4 months). RECORD-1 included patients who failed multiple lines of VEGF-targeted therapy, and received everolimus in third- and fourth-line setting. Conclusions: • TKIs increase PFS and/or OS as both first-line and second-line

treatments for clear-cell mRCC. LoE: 1b

- Axitinib has proven efficacy and superiority in PFS as a second-line treatment after failure of cytokines and VEGF-targeted therapy in comparison with sorafenib. LoE:1b
- Everolimus prolongs PFS in patients who have previously failed or are intolerant of VEGF-targeted therapy. LoE: 1b
- Sorafenib has broad activity in a spectrum of settings in clear-cell patients previously treated with cytokine or targeted therapies. 4
- Both mTOR inhibitors (everolimus and temsirolimus) and VEGF-targeted therapies (sunitinib or sorafenib) can be used in non-clear-cell RCC.

Table 7.3: EAU 2015 evidence-based recommendations for systemic therapy in patients with mRCC

RCC type	MSKCC risk group [323]	First-line	LE^	Second-line*	LE^	Third-line*	LE^	Later lines	LE
Clear cell*	Favourable, Intermediate and poor	sunitinib pazopanib bevacizumab + IFN Favourable-intermediate only)	1b 1b 1b	after VEGFR: axitinib sorafenib# everolimus after cytokines: sorafenib# axitinib pazopanib	 2a 2a 2a 1b 2a 2a	after VEGFR: everolimus after mTOR: sorafenib	 2a 1b	any targeted agent	4
Clear cell*	poor¶	Temsirolimus	1b	any targeted agent	4				
Non-clear-cell §	any	sunitinib everolimus temsirolimus	2a 2b 2b	any targeted agent	4				

IFN-α = interferon alpha; LE = level of evidence; MSKCC = Memorial Sloan-Kettering Cancer Center; mTOR = mammalian target of rapamycin inhibitor; RCC = renal cell carcinoma; TKI= tyrosine kinase inhibitor.

* Doses: IFN-α - 9 MU three times per week subcutaneously, bevacizumab 10 mg/kg biweekly intravenously; sunitinib 50 mg daily orally for 4 weeks, followed by 2 weeks of rest (37.5 mg continuous dosing did not show significant differences); temsirolimus 25 mg weekly intravenously; pazopanib 800 mg daily orally. Axitinib 5 mg twice daily, to be increased to 7 mg twice daily, unless greater than grade 2 toxicity, blood pressure higher than 150/90 mmHg, or the patient is receiving antihypertensive medication. Everolimus, 10 mg daily orally.

§ No standard treatment available. Patients should be treated in the framework of clinical trials or a decision can be made in consultation with the patient to perform treatment in line with ccRCC.

¶ Poor risk criteria in the NCT00065468 trial consisted of MSKCC [323] risk plus metastases in multiple organs.

Sorafenib was inferior to axitinib in a RCT in terms of PFS but not OS [351].

^ Level of evidence was downgraded in instances when data were obtained from subgroup analysis within an RCT.

Members of the Genitourinary Cancer Disease Site Group, 2011 [18].

Cancer Care Ontario

Fragestellung:

When compared to non-interleukin-2 containing regimens, is there a role for interleukin-2 (IL-2) in the treatment of patients with unresectable or metastatic renal cell carcinoma (RCC) for improving overall or progression-free survival, response rate, and quality of life considering its adverse effects?

Methodik

Interleukin-2 in the treatment of patients with unresectable or metastatic renal cell cancer	Grundlage der Leitlinie MEDLINE (1966 through February 2005), EMBASE (1980 through 2005 week 9), and CANCERLIT (1975 through October 2002) databases were searched for relevant papers. In addition, the Cochrane Library databases (2004, Issue 4) and the conference proceedings of the American Society of Clinical Oncology (1995-2005) and the American Urological Association (1995-2005) were searched for abstracts of relevant trials. Articles were selected for inclusion in this systematic review if they were fully published reports or abstracts of RCTs or meta-analyses of RCTs comparing IL-2–containing treatment regimens to regimens without IL-2 in patients with unresectable or metastatic RCC. Reports were required to provide data on at least one of the following outcomes: survival (i.e., overall, progression-free, or time-to-progression), response rate, toxicity, or quality of life.
	Empfehlungen • Non-high–dose IL-2–containing regimens should not be used as standard treatment for unresectable or metastatic RCC. • High-dose IL-2 should only be used by experienced physicians in the context of a clinical trial or investigational setting. In patients with unresectable or metastatic RCC, IL-2–containing immunotherapy does not provide superior treatment efficacy over non-IL-2 regimens, with added toxicity. There is evidence that IL-2 combined with IFN-a and chemotherapy (5-fluorouracil, fluorouracil) improves response rates and survival when compared to either agent alone or a non-immunotherapy control; however, those findings require confirmation in further, properly powered clinical trials with appropriate comparators (i.e., IFN-a) and should not be considered the standard of care. There are insufficient data to support the routine use of high-dose intravenous IL-2 therapy outside of a clinical trial or investigational setting, and its unique toxicity warrants its administration in specialized centres equipped to deal with specific toxicities and provide comprehensive care. <u>Evidenzbasis</u> Six randomized trials comparing IL-2–containing regimens to regimens without IL-2 form the evidence base of this review. Three trials had three arms, and three trials had two arms, providing a total of nine comparisons. Patient accruals ranged from 60 to 425 and totalled 1,098

	eligible randomized patients. Each trial assessed IL-2 combined with other agents, and two of three three-arm trials also assessed IL-2 as a single agent. IL-2 was studied in combination with interferon-alpha in each trial, either alone or with chemotherapy (e.g., fluorouracil or 5-fluorouracil) and 13-cis-retinoic acid or tamoxifen. No trials were identified that compared high-dose IL-2 to non-IL-2 regimens.
Canil C et al., 2013 [6]. **Cancer Care Ontario** Interferon-alfa in the Treatment of Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer	Fragestellung: Is interferon-alfa (IFN-α) an effective treatment option for patients with inoperable locally advanced or metastatic renal cell cancer (RCC)? Specifically, does it improve overall or progression-free survival, tumour response rate, and/or quality of life? What are its adverse effects?
	Methodik Grundlage der Leitlinie MEDLINE (1966 through May 2009) and EMBASE (1980 through 2009 week 19) were searched for relevant papers. In addition, the Cochrane Library databases (2009, Issue 2) and the meeting proceedings of the American Society of Clinical Oncology 1995-2008, the ASCO genitourinary symposia (2008-2009), and the American Urological Association (1995-2009) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearing House (http://www.guideline.gov/index.asp) were also searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by four reviewers, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles. Inclusion Criteria Report Types: Fully published RCTs, abstracts of RCTs, or meta-analyses that compared IFN-α-containing treatment regimens to regimens without IFN-α. Study Types: Randomized phase II and phase III studies. Patient Characteristics: Patients with inoperable locally advanced or metastatic RCC. RCTs including non-RCC patients were eligible as long as outcomes were analyzed separately for RCC patients. Outcomes: Reports were required to provide data on at least one of the following outcomes: response rate, survival (overall, progression-free,

	and time-to-progression), toxicity, and quality of life. Controls: Placebo; Cytotoxic chemotherapy was considered a potentially appropriate control therapy on the basis of lack of anti-tumour activity and patient benefit identified in clinical trials; Hormonal therapies such as medroxyprogesterone (MPA) were considered appropriate control therapies on similar grounds to chemotherapy; IFN-γ has been tested as a therapy for RCC but was considered as a control therapy equivalent to placebo for the purpose of this review. This assumption was considered justified by the results of a large RCT in RCC that reported no difference in objective response or survival when compared to placebo.
	Empfehlungen Ninety-eight unique RCTs of IFN-α were identified by the literature search, and eight of those met the eligibility criteria. The search also located two systematic reviews with meta-analyses. No evidence-based guidelines were identified. • Results from recent randomized trials indicate that inhibitors of angiogenesis such as sunitinib and temsirolimus are of superior clinical effectiveness to IFN-α and therefore are recommended as preferred treatment options. • When angiogenesis inhibitors are not available or not recommended, single-agent IFN-α improves survival and disease control compared to older alternative therapies (such as IFN-gamma [IFN-γ] or medroxyprogesterone acetate) and represents a potentially effective alternative treatment option. • The benefits of combined immunotherapy including IFN-α over IFN-α therapy alone are unclear, and this approach should not be routinely offered outside of clinical trials. KEY EVIDENCE • Meta-analyses of randomized clinical trials (RCTs) comparing IFN-α-based therapy with control treatment demonstrated an improvement in overall survival (six RCTs [n=992]; hazard ratio=0.79; 95% confidence interval, 0.69-0.91) with IFN-α-based therapy. This is equivalent to a 21% reduction in the risk of death over the time course of the RCTs included in this analysis. • In a large RCT comparing IFN-α alone to medroxyprogesterone, lack of appetite, tiredness, nausea and vomiting, lack of energy, dry mouth, shivering, and depressed mood were more common with

	IFN-α therapy. • A Cochrane meta-analysis of four RCTs reported no difference with regards to efficacy between IFN-α2a and IFN-α2b. CONCLUSIONS Until recently, very few systemic therapeutic options existed for patients with inoperable locally advanced or metastatic RCC. Immunotherapy with IFN-α can be considered as a treatment option to modestly improve survival and disease control in this patient population. However, given the toxicity profile of IFN-α, patient factors such as age and performance status must be taken into consideration and may affect patients' ability to tolerate and benefit from therapy. Further, angiogenesis inhibitors have expanded the treatment repertoire for RCC and appear to have superior effectiveness compared to IFN-α. In view of this, the role of IFN-α in the treatment of RCC is less clear. However, as not all patients may have access to the newer therapies due to their costs, information about the effectiveness of IFN-α is still of value. Locally advanced or metastatic RCC remains an incurable disease, current treatments remain palliative, and further research is warranted. Whenever possible, patients should be encouraged to participate in clinical trials.
Hotte S et al., 2009 [11]. **Cancer Care Ontario** The Use of Inhibitors of Angiogenesis in Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer: Guideline Recommendations (reviewed	Fragestellung: In adult patients with inoperable locally advanced or metastatic renal cell cancer (RCC): 1. Does treatment with inhibitors of angiogenesis improve overall (OS) and/or progression-free survival (PFS)? Secondary outcomes of interest include quality of life (QOL), objective tumour response rate, clinical response rate, and adverse effects. 2. Is a combination of inhibitors of angiogenesis better than any single-agent angiogenesis inhibitor? 3. Does sequential administration of a second inhibitor of angiogenesis offer additional benefit to patients?
	Methodik Grundlage der Leitlinie Relevant articles were identified by searches of MEDLINE (2001 – February 2008 week 2), EMBASE (2001 – 2008 week 8), and the

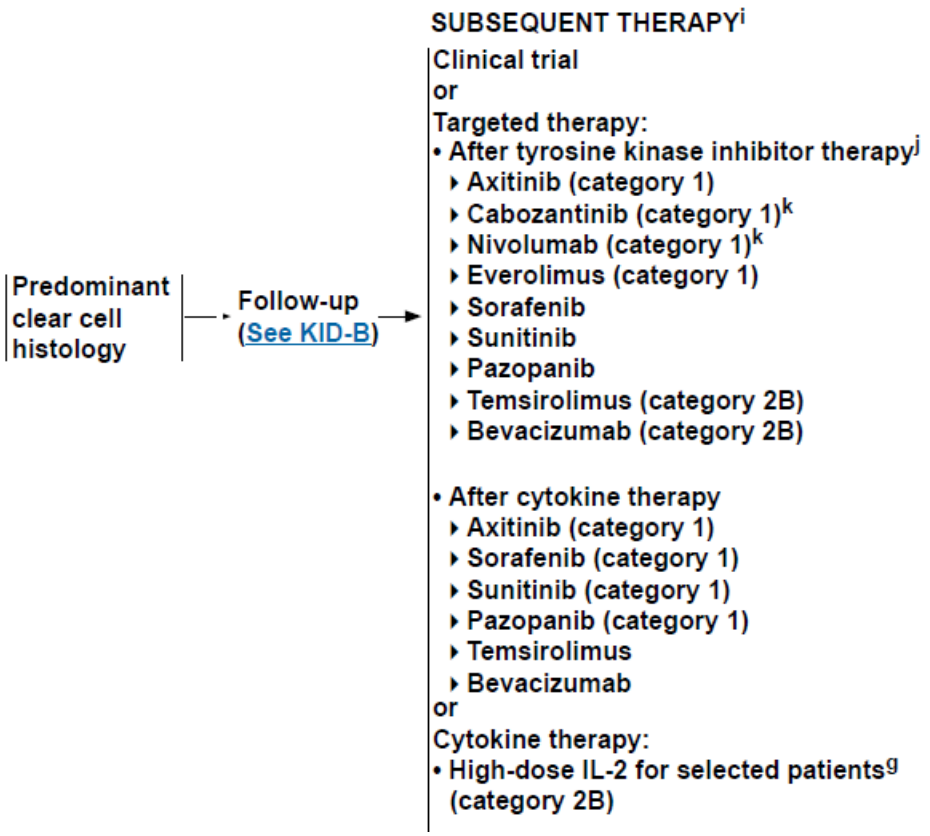
2013)	Cochrane Library (2007, Issue 4). The conference proceedings of the annual meetings of the American Society of Clinical Oncology (2002-2008), including the Genitourinary Cancer Symposium (2008), the European Society of Medical Oncology (2002-2007), and the European Cancer Conference (2003, 2005, and 2007) were also searched for relevant trials. Where relevant abstracts were identified, supplementary online resources (i.e., slides from accompanying presentations) were also searched for additional data. The reference lists of eligible trials were searched for relevant articles, and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) was searched for existing evidence-based practice guidelines. Expert colleagues were also asked to identify any relevant unpublished or published trials not otherwise identified. Study Selection Criteria Articles were eligible for inclusion into the systematic review if they met the following criteria: • They were randomized controlled trials (RCTs) (published or unpublished, full articles or abstracts) comparing: An angiogenesis inhibitor to placebo, IFN-a, or IL-2; A combination of angiogenesis inhibitors to any single-agent angiogenesis inhibitor; Sequential administration of a second angiogenesis inhibitor to any single-agent angiogenesis inhibitor • They reported on at least one of the following outcomes: OS, PFS, QOL, objective tumour response rate, clinical response rate, or adverse effects. • They were systematic reviews or evidence-based clinical practice guidelines that addressed any of the research questions. • They were published in English, as translation capabilities were not available.
	Empfehlungen RECOMMENDATIONS Immunotherapy with or without cytoreductive nephrectomy has been the standard of care in patients with inoperable locally advanced or metastatic RCC. There is now evidence of important clinical benefit for agents that inhibit angiogenesis in this patient population. Everolimus is recommended as second- or third-line therapy in patients previously treated with sunitinib, sorafenib, or both, based on a 70%

	reduction in the risk of disease progression. Sorafenib should be considered a treatment option in patients who progress following initial immunotherapy, based on a 56% reduction in the risk of disease progression or death reported with second-line therapy in patients with favourable1- to intermediate-risk disease previously treated with immunotherapy. KEY EVIDENCE Second-line treatment: Sorafenib – the largest trial (n=903), comparing sorafenib to placebo in patients who had failed prior immunotherapy, reported sorafenib significantly prolonged PFS over placebo (median, 5.5 months vs. 2.8 months; HR=0.44; 95% CI, 0.35 to 0.55; p<0.001). OS, the primary endpoint, was analyzed just prior to treatment crossover after 6.6 months of follow-up; sorafenib was associated with a 28% reduction in the risk of death compared to placebo (HR=0.72; 95% CI, 0.54 to 0.94; p=0.02). However, this result did not reach the threshold set for statistical significance (p<0.0005). Grade 3/4 hypertension (p<0.001) and hand-foot skin reactions (p<0.001), and cardiac ischemia or infarction (3% vs. 1%) were more common with sorafenib. Serious adverse events leading to hospitalization or death occurred in 34% of patients receiving sorafenib and 24% of patients receiving placebo (p<0.01). No differences in overall QOL were detected between the two arms, although sorafenib improved the following symptoms: cough, fever, worry that condition will worsen, shortness of breath, and ability to enjoy life. Poor-risk patients were not included in this trial. Bevacizumab – one randomized phase II trial (n=116) reported longer time-to-disease progression with low-dose bevacizumab (median, 4.8 months; HR=2.55; p<0.001) and a marginal benefit with high-dose bevacizumab (median, 3 months; HR=1.26; p=0.053) compared to placebo (median, 2.5 months). No differences in OS were observed between treatment arms. Second- or third-line treatment: Everolimus – one phase III trial (n=410) compared everolimus to placebo in patients who had progressed on either sunitinib or sorafenib or both. PFS was significantly prolonged with everolimus compared with placebo (HR=0.30; 95% CI, 0.22 to 0.40; p<0.0001). No significant difference in OS was observed. However, 81% of patients in the placebo control arm

	crossed over to everolimus therapy at the time of disease progression. Compared with placebo, everolimus was associated with higher rates of grade 3/4 stomatitis, infections and non-infectious pneumonitis, and caused more adverse effects leading to treatment discontinuations and dose reductions. No differences in health-related QOL were observed between trial arms. DISCUSSION Second-line Treatment To date, only three trials evaluating inhibitors of angiogenesis in the second-line setting have reported results. The first trial randomized 903 patients to sorafenib or placebo in patients with favourable- or intermediate-risk RCC who had progressed on prior systemic therapy. Median PFS was almost doubled in patients receiving sorafenib, from approximately three months to six months. OS was also improved, but this benefit did not reach statistical significance. Owing to the unplanned crossover of patients in this trial, it is likely a statistically significant survival result will not be observed. Sorafenib did not adversely affect QOL, but improvements in a number of symptoms, such as dyspnea and ability to enjoy life were observed. The adverse effects associated with sorafenib in the second-line setting were similar to those observed in the trial that examined this agent as first-line therapy (discussed above). Because of its proven efficacy and its favourable toxicity profile, sorafenib should be offered as second-line treatment in patients with favourable- to intermediate-risk RCC. In the second trial, bevacizumab (high-dose vs. low-dose) was compared to placebo in 116 patients. No differences were reported in OS between treatment arms, and modest improvements in PFS were observed in the low-dose bevacizumab arm compared to placebo. At this time, bevacizumab is not recommended for use as either first-line or second-line therapy in patients with inoperable locally advanced or metastatic RCC. Sunitinib has not been compared in a randomized trial in the second-line setting. However, two phase II trials evaluated the efficacy of sunitinib in patients who had progressed despite previous cytokine therapy. Each trial entered 63 and 106 patients; median-PFS times were 8.7 months and 8.3 months with partial response rates of 40% and 34%, respectively. In each trial, a further 27% and 29% of patients experienced stable disease for three months or longer. Based on this

	information, and the proven efficacy of this agent in the first-line setting, it is the expert opinion of the GU DSG that sunitinib is likely an acceptable treatment option in the second-line setting. Phase III-level data on the second-line use of sunitinib would be preferred in order to make treatment recommendations but are unlikely to be conducted given the positive results observed in the first-line setting. Everolimus is the only agent that has been evaluated in the modern TKI era as a second-line therapy. Motzer et al recently published results of a RCT comparing everolimus to placebo as second- or third-line therapy in patients who had progressed on a VEGFR TKI inhibitor. The primary outcome was PFS, and crossover to everolimus was permitted upon disease progression. The trial was stopped early for benefit and showed an improvement in PFS from 1.9 to four months, with an HR of 0.30 ($p<0.0001$). No difference in OS was observed; however, this is likely because 81% of patients in the placebo arm crossed over to everolimus (most of them at the two-month efficacy assessment). Everolimus was generally well tolerated. Slightly more grade 3 and 4 adverse events were observed inpatients receiving everolimus, but only 4% of patients required a dose reduction. Based on these results, everolimus can now be considered the standard second- or third-line agent after failure of VEGFR TKI agents such as sunitinib. It is currently the only agent that has shown benefit in that setting; all other trials of second-line therapy have been performed in patients who had progressed on other first-line treatments such as immunotherapy.
National Comprehensive Cancer Network (NCCN),	Fragestellung: Leitlinie des National Comprehensive Cancer Network
	Methodik

2016 [19]. NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer, Version 3.2016	Prior to the update of this version of the NCCN Guidelines for Kidney Cancer, an electronic search of the PubMed database was performed to obtain key literature in Kidney Cancer published between 07/28/14 and 07/28/15, using the following search terms: Renal Cell Carcinoma or Kidney Cancer. An update search was carried out before the publication of this document. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[17] The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The PubMed search resulted in 364 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and/or discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Any recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion. The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website. LoE und GoR Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. Falls nicht anders angegeben, entsprechen alle Empfehlungen der Kategorie 2A
	Empfehlungen

	
Alberta Provincial Genitourinary Tumour Team, 2013 [1]. **Alberta Health Services** Renal cell carcinoma	Fragestellung: • What are the appropriate diagnostic tests for renal cell carcinoma? • How should renal cell carcinoma be managed (i.e., surgically)? • What is the role of systemic therapy and radiotherapy in the management of renal cell carcinoma? • Are there other therapies that have shown benefit for patients with renal cell carcinoma? • What are the appropriate follow up strategies for renal cell carcinoma?
	Methodik Grundlage der Leitlinie – The guideline was developed in 2005 and then updated in 2009, 2010, 2011, 2012, and 2013. The 2013 literature update was performed on 2013 May 3 and resulted in a total of 82 citations, of which 41 were considered relevant.

	– Search Strategy • Cochrane and National Guidelines Clearinghouse databases, as well as individual guideline developers' websites were searched for evidence relevant to this topic. The MEDLINE and EMBASE databases were searched for evidence relevant to this topic. The search strategy included the term "renal cell carcinoma" and limited the results to clinical trials published in English. Articles were further excluded if they were phase I, included fewer than ten patients, were non-treatment related (i.e. pathology/staging, imaging, genetics, prevention, etc.), were retrospective without a comparison group, did not include adult patients, or did not look at survival, recurrence or quality of life outcomes. – Formulating Recommendations • The GWG members formulate the guideline recommendations based on the interpretation of evidence synthesized by the KMS during the planning process blended with expert clinical experience and local context. The GWG members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution with revisions, or develop their own set of recommendations. The degree to which a recommendation is based on expert opinion of the GWG and/or the Provincial Tumour Team members will be explicitly stated in the guideline recommendations. Ideally recommendations should be presented in a standardized format explicitly detailing appropriate actions and the circumstances in which they should be applied. – Evidence Foundations and Strength of Recommendations. • Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations 5 GURU does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations including: ○ Description of all known benefits and possible harms ○ Evidence summary, quality/quantity/consistency of discussion ○ Discussion of the role of clinical experience, theory, values and opinions in developing the recommendation

	Empfehlungen **Advanced Stage Disease** <u>Systematic Therapy</u> For patients with advanced, node positive, and/or unresectable or metastatic disease, systemic is indicated. <u>Second-line Therapy</u> Sorafenib is indicated for second-line treatment of renal cell carcinoma, after cytokine failure. In a randomized phase III trial, sorafenib was shown to be superior to best supportive care (placebo) with regards to median progression-free survival (5.5 vs. 2.8 months; p<.01) and survival (hazard ratio for death, 0.72; p=.02). Partial responses (as the best response) were seen in 10% of patients receiving sorafenib and in 2% of those receiving placebo (p<.001). profile of sorafenib (i.e. diarrhea, rash, fatigue, alopecia, and hand-foot skin reactions) and follow patients accordingly with experienced nursing support. Doses and treatment intervals should be modified as per the patient's toxicity. Long term efficacy and safety of sorafenib has been established: patients (n=169) who were treated for more than one year with sorafenib achieved a median progression free survival of 10.9 months and a disease control rate of 92% with no unexpected toxicities associated with long-term use. Physicians should be aware of the toxicity until post-cross-over placebo survival data were censored (17.8 vs.14.3 months; p=.029). However, overall survival was not significantly different (17.8 vs.15.2 months; p=.146) In subgroup analyses, both high-vascular endothelial growth factor (VEGF; p<.01) and low-VEGF (p<.01) patients benefited from sorafenib. <u>Evidence</u> 16. Escudier B, Szczylik C, Demkow T. Randomized phase II trial of the multi-kinase inhibitor sorafenib versus interferon (IFN) in treatment-naive patients with renal cell carcinoma (mRCC). J Clin Onco 2006;24:217s. 17. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009 Jul 10;27(20):3312-3318. 18. Ratain MJ, Eisen T, Stadler WM, Flaherty KT, Kaye SB, Rosner GL, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2006 Jun 1;24(16):2505-2512. 41. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007 Jan 11;356(2):125-134. 42. Hutson TE, Bellmunt J, Porta C, Szczylik C, Staehler M, Nadel A, et al. Long-term safety of sorafenib in advanced renal cell carcinoma: follow-up of patients from phase III TARGET. Eur J Cancer 2010 Sep;46(13):2432-2440.

	Everolimus is indicated for second-line therapy of metastatic renal cell carcinoma, only after progression on sunitinib, sorafenib, or both based on phase III data demonstrating superior progression-free survival to best supportive care. Finally, efficacy results among patients with metastatic renal cell carcinoma treated with either everolimus (10 mg/day; n=277) plus best supportive care or placebo plus best supportive care (n=139) demonstrated an advantage in median progression free survival (4.9 vs.1.9 months; p<.001) but not median overall survival (14.8 vs.14.4 months; p=.162) although it should be noted that this study did allow crossover to everolimus at the time of progression. The toxicity profile for everolimus includes infections, dyspnea, pneumonitis and fatigue. Evidence 43. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomized, placebo-controlled phase III trial. Lancet 2008 Aug 9;372(9637):449-456. 44. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. Cancer 2010 Sep 15;116(18):4256-4265. 45. White DA, Camus P, Endo M, Escudier B, Calvo E, Akaza H, et al. Noninfectious pneumonitis after everolimus therapy for advanced renal cell carcinoma. Am J Respir Crit Care Med 2010 Aug 1;182(3):396-403. Another promising drug for second-line therapy for metastatic renal cell carcinoma is axitinib, a selective second-generation inhibitor of VEGF receptors. It has shown positive results in a phase III trial compared with sorafenib. The 723 patients included in the study had confirmed renal cell carcinoma that progressed despite first-line therapy containing sunitinib, bevacizumab plus interferon-alfa, temsirolimus, or cytokines.Median progression-free survival was 6.7 months for axitinib versus 4.7 months in patients receivingsorafenib, with non-significant differences regarding toxicity. Evidence 46. Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 2011 Dec 3;378(9807):1931-1939.
Bellmunt J et al., 2014 [3]. **SEOM** SEOM	Fragestellung: Sociedad Española de Oncología Médica (SEOM) Diagnosis and treatment of renal cell carcinoma
	Methodik

clinical guidelines for the treatment of renal cell carcinoma	LoE and grades of recommendation (adapted from the Infectious Disease Society of America-United States Public Health Service Grading System) Levels of evidence I Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity III Prospective cohort studies IV Retrospective cohort studies or case–control studies V Studies without control group, case reports, experts' opinions Grades of recommendation A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional D Moderate evidence against efficacy or for adverse outcome, generally not recommended E Strong evidence against efficacy or for adverse outcome, never recommended Anmerkung: Die Leitlinie entspricht nicht vollständig den Anforderungen an eine S3 Leitlinie und wird ergänzend dargestellt. Es fehlen Angaben zur Literaturrecherche.
	Empfehlungen **Management of advanced metastatic disease: first-line, second-line and therapeutic sequences—therapeutic algorithm** *Second-line treatment and therapeutic sequences* 1. After progression to first-line therapy with a TKI, sequential administration of alternative targeting agents should be considered (level of evidence: I; grade of recommendation: A). In this setting, both sequences either administering a second TKI or mTOR inhibitor are active therapeutic alternatives (LoE/GoR: I, B for everolimus and

	I, B for axitinib). 2. Axitinib has been shown to be superior to sorafenib in second-line treatment (LoE/GoR: I, A), but sorafenib could be even consider an active option (LoE/GoR: IV, B). 3. Sequential therapy with mTOR inhibitors should be considered in patients who progress after a second TKI (LoE/GoR: III, B) or in those patients who experienced poor tolerance to a first-line TKI (LoE/GoR: IV, B). Evidence 40. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356(2):125–34. 41. Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011;378(9807):1931–9. 42. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008;372(9637):449–56. 43. Hutson TE, Escudier B, Esteban E, Bjarnason GA, Lim HY, Pittman KB, et al. Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2014;32(8):760–7. 44. Bellmunt J, Pons F, Foreshew A, Fay AP, Powles T, Porta C, et al. Sequential targeted therapy after pazopanib therapy in patients with metastatic renal cell cancer: efficacy and toxicity. Clin Genitourin Cancer. 2014;12(4):262–9. 45. Calvo E, Grünwald V, Bellmunt J. Controversies in renal cell carcinoma: treatment choice after progression on vascular endothelial growth factor-targeted therapy. Eur J Cancer. 2014;50(7):1321–9. Treatment algorithm

	<table><tr><th>Treatment status</th><th>Setting</th><th>Category I evidence</th><th>Category II evidence</th></tr><tr><td rowspan="4">Treatment naive (ccRCC)</td><td rowspan="3">Good intermediate risk</td><td>Sunitinib</td><td>Sorafenib</td></tr><tr><td>Bevacizumab/ Interferon</td><td>High dose IL-2</td></tr><tr><td>Pazopanib</td><td></td></tr><tr><td>Poor risk</td><td>Temsirolimus</td><td>Sunitinib Sorafenib</td></tr><tr><td rowspan="4">Second-line (ccRCC)</td><td rowspan="2">Cytokine refractory</td><td>Sorafenib Pazopanib Sunitinib</td><td></td></tr><tr><td>Axitinib</td><td></td></tr><tr><td>TKI failure</td><td>Everolimus Axitinib</td><td>Sorafenib</td></tr><tr><td>Prior mTor inhibitors</td><td></td><td>Sunitinib</td></tr><tr><td>Non-Clear Cell histology</td><td></td><td></td><td>Temsirolimus Everolimus Sunitinib Sorafenib</td></tr></table>
Benahmed N. et al., 2015 [4]. **Belgian Health Care Knowledge Centre (KCE)** Renal cancer in adults: diagnosis, treatment and follow-up	Fragestellung: Belgian Health Care Knowledge Centre (KCE) This guideline provides recommendations based on current scientific evidence for the diagnosis, treatment, follow-up and supportive care of patients with renal cancer.
	Methodik Grundlage der Leitlinie – Firstly, clinical questions were developed in collaboration with members of the Guideline Development Group. Secondly a literature review was conducted (including a search for recent, high quality guidelines). Thirdly, on the basis of the results of the literature review, recommendations were formulated and graded according to the GRADE approach. – Search period for guidelines: no limits; for other publications (systematic reviews, meta-analysis, individual RCT): ≥ 2009-2014 – We first looked for high quality guidelines based on a valid and sufficiently documented systematic search and reporting of the

underlying evidence; in some cases, comprehensive guidelines are only based on a systematic review for a part of the clinical questions, as resources often are not sufficient to cover all clinical recommendations. In this case, we only took over recommendations based on a systematic search of the evidence. We mentioned this per clinical question.

- For each research question, a search for systematic reviews was conducted in MEDLINE, Embase and the Cochrane Library (Cochrane Database of Renal cancer in adults Systematic Reviews, DARE and HTA database). If a recent high quality systematic review was available, a search for primary studies published after the search date of the review was performed in MEDLINE, Embase and CENTRAL. If more than one systematic review was identified for a particular research question, the focus was on the most complete systematic review. If no systematic review was available, a search for primary studies was performed in those databases. Members of the guideline development group (GDG) were also consulted to identify additional relevant evidence that may have been missed by the search.
- Quality appraisal: Critical appraisal of each study was performed by a single KCE expert. In case of doubt, a second KCE expert was consulted. The AGREE II instrument was used to evaluate the methodological quality of the identified international guidelines.
- The quality appraisal of RCTs for therapeutic interventions was performed using the "Cochrane Collaboration's tool for assessing risk of bias".

LoE

Table 1 – A summary of the GRADE approach to grading the quality of evidence for each outcome

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖) Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)
Observational studies	Low			

Source: Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311-6.

Table 2 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect.	RCTs without important limitations or overwhelming evidence from observational studies.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	RCTs with very important limitations or observational studies or case series.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.	

Source: Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

GoR

The strength of each recommendation was assigned using the GRADE system. The strength of recommendations depends on a balance between all desirable and all undesirable effects of an intervention (i.e., net clinical benefit), quality of available evidence, values and preferences, and estimated cost (resource utilization).

Table 4 – Strength of recommendations according to the GRADE system

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects *(the intervention is to be put into practice)*, or the undesirable effects of an intervention clearly outweigh the desirable effects *(the intervention is not to be put into practice)*.
Weak	The desirable effects of an intervention probably outweigh the undesirable effects *(the intervention probably is to be put into practice)*, or the undesirable effects of an intervention probably outweigh the desirable effects *(the intervention probably is not to be put into practice)*.

Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35.

Table 5 – Factors that influence the strength of a recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted.
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted.
Costs (resource allocation)	The higher the costs of an intervention, i.e. the greater the resources consumed, the lower the likelihood that a strong recommendation is warranted.

Sources: Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A et al. An Official ATS Statement: Grading the Quality of Evidence and Strength of Recommendations in ATS Guidelines and Recommendations. Am J Respir Crit Care Med 2006; 174:605–14. – Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B et al. Grading Strength of Recommendations and Quality of Evidence in Clinical Guidelines - Report From an American College of Chest Physicians Task Force. Chest 2006; 129:174-81.

Empfehlungen

Targeted therapy

<u>Second-line treatment</u>

	Sorafenib can be considered as second-line treatment in clear cell metastatic renal cell carcinoma. (LoE High, Strength of Recommendation Strong) Evidence 112. Escudier B, Eisen T, Stadler W, Szcylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356:125-34. 154. Ratain MJ, Eisen T, Stadler WM, Flaherty KT, Kaye SB, Rosner GL, et al. Phase II placebo controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. Journal of Clinical Oncology 2006;24(16):2505-12. 155. Bukowski R, Cella D, Gondek K, B E. Effects of sorafenib on symptoms and quality of life. Results from a large randomized placebo-controlled study in renal cancer. American Journal of Clinical Oncology 2007;30:220–7. 156. Eisen T, Oudard S, Szczylik C, Gravis G, Heinzer H, Middleton R, et al. Sorafenib for older patients with renal cell carcinoma: subset analysis from a randomized trial. Journal of the National Cancer Institute. 2008;100(20):1454-63. 157. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. Journal of clinical oncology. 2009;27(20):3312-8. 158. Antoun S, Birdsell L, Sawyer MB, Venner P, Escudier B, Baracos VE. Association of skeletal muscle wasting with treatment with sorafenib in patients with advanced renal cell carcinoma: results from a placebo-controlled study. Journal of clinical oncology. 2010;28(6):1054-60. 159. Negrier S, Jäger E, Porta C, McDermott D, Moore M, Bellmunt J, et al. Efficacy and safety of sorafenib in patients with advanced renal cell carcinoma with and without prior cytokine therapy, a subanalysis of TARGET. Medical oncology Northwood, London, England). 2010;27(3):899-906. 160. Hutson TE, Bellmunt J, Porta C, Szczylik C, Staehler M, Nadel A, et al. Long-term safety of sorafenib in advanced renal cell carcinoma: follow-up of patients from phase III TARGET. European journal of cancer (Oxford, England : 1990). 2010;46(13):2432-40. Everolimus can be considered in metastatic renal cell carcinoma patients previously treated with Vascular endothelial growth factor (VEGF)-pathway targeted therapy (i.e. bevacizumab, sunitib, sorafenib,…) or cytokines (IFN-α, IL-2). (LoE Low, Strength of Recommendation Strong) Evidence 119. Motzer RJ, Escudier B, Oudard S, Porta C, Hutson TE, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008;372:449-56. 165. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. Cancer. 2010;116(18):4256-65. 166. White DA, Camus P, Endo M, Escudier B, Calvo E, Akaza H, et al. Noninfectious pneumonitis after everolimus therapy for advanced renal cell carcinoma. American journal of respiratory and critical care medicine. 2010;182(3):396-403. 167. Beaumont JL, Butt Z, Baladi J, Motzer RJ, Haas T, Hollaender N, et al. Patient-reported outcomes in a phase iii study of everolimus versus placebo in patients with metastatic carcinoma of the kidney that has progressed on vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy. Oncologist. 2011;16(5):632-40. 168. Tsukamoto T, Shinohara N, Tsuchiya N, Hamamoto Y, Maruoka M, Fujimoto H, et al. Phase III trial of everolimus in metastatic renal cell carcinoma: subgroup analysis of Japanese patients from RECORD-1. Japanese journal of clinical oncology.

	2011;41(1):17-24. 169. Bracarda S, Hutson TE, Porta C, Figlin RA, Calvo E, Grunwald V, et al. Everolimus in metastatic renal cell carcinoma patients intolerant to previous VEGFr-TKI therapy: A RECORD-1 subgroup analysis. Br. J. Cancer. 2012;106(9):1475-80. 170. Calvo E, Escudier B, Motzer RJ, Oudard S, Hutson TE, Porta C, et al. Everolimus in metastatic renal cell carcinoma: Subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study. Eur. J. Cancer. 2012;48(3):333-9. 171. Porta C, Calvo E, Climent MA, Vaishampayan U, Osanto S, Ravaud A, et al. Efficacy and safety of everolimus in elderly patients with metastatic renal cell carcinoma: an exploratory analysis of the outcomes of elderly patients in the RECORD-1 Trial. European urology. 2012;61(4):826-33. 172. Blesius A, Beuselinck B, Chevreau C, Ravaud A, Rolland F, Oudard S, et al. Are tyrosine kinase inhibitors still active in patients with metastatic renal cell carcinoma previously treated with a tyrosine kinase inhibitor and everolimus? Experience of 36 patients treated in France in the RECORD-1 Trial. Clinical genitourinary cancer. 2013;11(2):128-33. Axitinib is recommended in metastatic renal cell carcinoma patients previously treated with VEGF-pathway targeted therapy or cytokines. Note: Axitinib is reimbursed after a failure of first line treatment with TKI or cytokine. LoE Low, Strength of Recommendation Strong) Evidence 173. Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011;378(9807):1931-9. 174. Cella D, Escudier B, Rini B, Chen C, Bhattacharyya H, Tarazi J, et al. Patient-reported outcomes for axitinib vs sorafenib in metastatic renal cell carcinoma: phase III (AXIS) trial. British journal of cancer. 2013;108(8):1571-8. 175. Motzer RJ, Escudier B, Tomczak P, Hutson TE, Michaelson MD, Negrier S, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet oncology. 2013;14(6):552-62. 176. Ueda T, Uemura H, Tomita Y, Tsukamoto T, Kanayama H, Shinohara N, et al. Efficacy and safety of axitinib versus sorafenib in metastatic renal cell carcinoma: subgroup analysis of Japanese patients from the global randomized Phase 3 AXIS trial. Japanese journal of clinical oncology. 2013;43(6):616-28. 177. Rini BI, Quinn DI, Baum M, Wood LS, Tarazi J, Rosbrook B, et al. Hypertension among patients with renal cell carcinoma receiving axitinib or sorafenib: analysis from the randomized phase III AXIS trial. Targeted Oncol. 2014:1-9. Third-line treatment Everolimus or sorafenib can be considered in third-line therapy. (LoE Very low, Strength of Recommendation Weak) Evidence 126. Motzer RJ, Porta C, Vogelzang NJ, Sternberg CN, Szczylik C, Zolnierek J, et al. Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: An open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(3):286-96.
Dutch	Fragestellung:

<table>
<tr><td>Dieticians Oncology Group, 2012 [8].
Renal cell carcinoma</td><td>Integraal kankercentrum Nederland (iKNL) / Urological Tumours National Working Group

This guideline is intended for all professionals involved in diagnostics, treatment and guidance of patients with renal cell carcinoma, such as general practitioners, urologists, medical oncologists, anaesthesiologists, radiotherapists, radiologists, pathologists and nuclear medicine physicians, pharmacists, psychologists, oncology nurses and consultants of comprehensive cancer centres.</td></tr>
<tr><td></td><td>Methodik

Grundlage der Leitlinie

– Update of the 2006 guideline and revision of the 2010 guideline
– Suche bis 2009, Recherchestrategie ist angegeben
– Search strategies
• Searches were made in Medline and the Cochrane database of systematic reviews for articles in English and Dutch. A search was also made in CINAHL regarding the clinical question concerning a fixed point of contact. A separate search strategy was used for each clinical question. Searches were made for publications in the English or Dutch language. Articles were also selected from reference lists of articles that had already been found.

LoE

Table 1: Level of evidence for conclusions based on the evidence underlying the conclusions
<table><tr><th>Level of evidence</th><th>Conclusion based on</th><th>Formulation</th></tr><tr><td>1</td><td>1 systematic review (A1) or at least 2 independently conducted A1- or A2-level studies</td><td>There is proof that.. you must...</td></tr><tr><td>2</td><td>At least 2 independently conducted B-level studies</td><td>It is plausible that... you should....</td></tr><tr><td>3</td><td>At least 1 A2-, B-, or C-level study</td><td>There are indications... you could</td></tr><tr><td>4</td><td>Expert opinion from, for example, working group members</td><td>It is the opinion of the guideline development group that...</td></tr></table>
GoR</td></tr>
</table>

Table Checklist for grading of recommendations

Conclusion on level of evidence	*Remaining considerations*	*Type of recommendation*	*Formulation*
1 or 2 High level of evidence	Strengthened conclusion or is neutral	Strong recommendation	There should....
1 or 2 High level of evidence	Weakened conclusion	Recommendation	It is recommended...
3 or 4 Low level of evidence	Strengthened conclusion or is neutral	Recommendation	It is recommended...
3 or 4 Low level of evidence	Weakened conclusion	No recommendation	A recommendation cannot be made. Optional: the development group is of the opinion that...

In practice, there may be multiple conclusions per clinical question, with different levels of evidence. If multiple conclusions have been formulated for a clinical question, the level of evidence of the conclusion that is of most importance to formulation of the recommendation has been included in the checklist 'Grading of Recommendations'.

Empfehlungen

Treatment of local recurrence/metastases - Systemic therapy

Second-line therapy

Recommendations:

In the case of patients with a good or intermediate prognosis metastatic clear cell renal cell carcinoma according to MSKCC criteria who have previously undergone first-line systemic therapy with a TKI (sunitinib or sorafenib), treatment should commence with second-line systemic therapy with the mTOR inhibitor everolimus.

In the case of patients with good or intermediate prognosis metastatic clear cell renal cell carcinoma according to MSKCC criteria who have previously undergone cytokine therapy, treatment should commence with systemic therapy in the form of the TKI sorafenib. An alternative is pazopanib.

The guideline development group is of the opinion that a metastatic non-clear cell renal cell carcinoma should be treated within a research context.

Table 1 Summary recommendations systemic therapy with metastatic renal cell carcinoma

RCC type	*MSKCC risk group*	*1st line therapy**	*2nd line therapy**	*3rd line therapy*
Clear cell	Good or intermediate	sunitinib IFN-a+bevacizumab pazopanib	everolimus after prior TKI	everolimus after prior TKI(s)
			sorafenib after prior cytokine therapy pazopanib after prior cytokine therapy	
	Poor	temsirolimus		
Non-clear cell	Good	**		
	Intermediate	**		
	Poor	**		
Remaining non-clear cell		**		

* Doses: IFN-a 9 MU 3 times per week subcutaneously, bevacizumab 10mg/kg biweekly intravenously; sunitinib 50 mg daily orally for a duration of 4 weeks, followed by 2 weeks of rest (37.5 mg continuously may be considered if the classic schedule is not tolerated as well); sorafenib 2 times daily 400 mg orally; temsirolimus 25 mg weekly intravenously; pazopanib 800 mg daily orally.

Conclusions:

It has been demonstrated that treatment with sorafenib for progression during or after immunotherapy results in an improvement in PFS in patients. (Level 1: A1)

Evidence

465 Coppin C, Le L, Porzsolt F, Wilt T. Targeted therapy for advanced renal cell carcinoma. Cochrane Database Syst Rev 2008 Apr 16;(2):CD006017.
475 Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007 Jan 11a;356(2):125-34.

It is plausible that treatment with everolimus for progression during or after 1 or 2 tyrosine kinase inhibitors results in an improvement in PFS in patients. (Level 2: A2)

Evidence

522 Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008 Aug 9;372(9637):449-56.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 30.03.2016**

# Suchschritt	Suchfrage
1	MeSH descriptor: [Carcinoma, Renal Cell] explode all trees
2	(renal and cell) or kidney* or nephroid* or hypernephroid* or grawitz* or (collecting next duct):ti,ab,kw (Word variations have been searched)
3	cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*:ti,ab,kw (Word variations have been searched)
4	#2 and #3
5	hypernephroma* or rcc:ti,ab,kw (Word variations have been searched)
6	#1 or #4 or #5
7	#1 or #4 or #5 Publication Year from 2011 to 2016, in Cochrane Reviews (Reviews only), Other Reviews and Technology Assessments

SR, HTAs in Medline (PubMed) am 30.03.2016

# Suchschritt	Suchfrage
1	carcinoma, renal cell[MeSH Terms]
2	(((((((renal[Title/Abstract]) AND cell[Title/Abstract])) OR kidney*[Title/Abstract]) OR nephroid*[Title/Abstract]) OR hypernephroid*[Title/Abstract]) OR grawitz*[Title/Abstract]) OR collecting duct[Title/Abstract]
3	((((((cancer*[Title/Abstract]) OR tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR neoplas*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR malignan*[Title/Abstract]
4	(#2) AND #3
5	(hypernephroma*[Title/Abstract]) OR rcc[Title/Abstract]
6	((#1) OR #4) OR #5
7	((((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR

	treated[Title/Abstract]) OR management[Title/Abstract]) OR treat*[Title/Abstract]) OR drug*[Title/Abstract]
8	(#6) AND #7
9	"Carcinoma, Renal Cell/therapy"[Mesh]
10	(#8) OR #9
11	(Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
12	(((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
13	(#11) OR #12
14	(#10) AND #13
15	(#14) AND ("2011/03/01"[PDAT] : "2016/03/30"[PDAT])

Leitlinien in Medline (PubMed) am 30.03.2016

# Suchschritt	Suchfrage
1	carcinoma, renal cell[MeSH Terms]
2	"Kidney Neoplasms"[Mesh:NoExp]
3	(((((((renal[Title/Abstract]) AND cell[Title/Abstract])) OR kidney*[Title/Abstract]) OR nephroid*[Title/Abstract]) OR hypernephroid*[Title/Abstract]) OR grawitz*[Title/Abstract]) OR collecting duct[Title/Abstract]
4	((((((cancer*[Title/Abstract]) OR tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR neoplas*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR malignan*[Title/Abstract]
5	(#3) AND #4

6	(hypernephroma*[Title/Abstract]) OR rcc[Title/Abstract]
7	(((#1) OR #2) OR #5) OR #6
8	(((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]) OR recommendation*[Title]
9	(#7) AND #8
10	(#9) AND ("2011/03/01"[PDAT] : "2016/03/30"[PDAT])

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