Abteilung Fachberatung Medizin

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

Vorgang: 2016-B-035 Lenvatinib

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I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Lenvatinib 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.	*Radiotherapie (bei inoperablen Metastasen)*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	*Beschluss über die Nutzenbewertung nach §35a SGB V vom 21. März 2013: Axitinib*
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 Beratungsanforderung/Fachinformation)
Zu prüfendes Arzneimittel:	
Lenvatinib	Anwendungsgebiet laut Positive Opinion vom 21.07.2016: Kisplyx ist indiziert in Kombination mit Everolimus zur Behandlung von erwachsenen Patienten mit fortgeschrittenem Nierenzellkarzinom (renal cell carcinoma, RCC) nach einer vorhergehenden, gegen den vaskularen endothelialen Wachstumsfaktor (VEGF) gerichteten Behandlung.
mTOR-Inhibitoren	
Everolimus L01XE10 z.B. Afinitor®	Nierenzellkarzinom 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. (FI Afinitor ®, März 2015)
Tyrosin-Kinase-Inhibitoren (TKI)	
Sunitinib L01XE04 SUTENT®	Metastasierte Nierenzellkarzinome (mRCC) SUTENT wird bei Erwachsenen zur Behandlung **fortgeschrittener/ metastasierter** Nierenzellkarzinome (mRCC) eingesetzt. (FI SUTENT®, Juni 2015)
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.** (FI Inlyta®, Mai 2015)

Pazopanib L01XE11 Votrient®	<u>Nierenzellkarzinom (RCC)</u> 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. (FI Votrient®, Mai 2015)
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. (FI Nexavar®, November 2014)
Zytokine	
Interferon alfa-2a L03AB04 Roferon®-A	Roferon-A wird für die Behandlung der folgenden Erkrankungen angewendet: - **Fortgeschrittenes** Nierenzell-Karzinom. (FI Roferon®-A, Juni 2015)
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. (FI PROLEUKIN® S, September 2014)

Quellen: AMIS-Datenbank, Fachinformationen

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

Inhalt

Indikation für die Recherche bei Wirkstoff (evtl. Markenname):

Lenvatinib ist in Kombination mit Everolimus indiziert zur Behandlung von Patienten mit inoperablem, fortgeschrittenem oder metastasiertem Nierenzellkarzinom nach einer gegen VEGF gerichteten Therapie.

Berücksichtigte Wirkstoffe/Therapien:

siehe Unterlage zur Beratung in AG: Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation fortgeschrittenes oder metastasiertes 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. 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 ergaben diese 18 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen:

Akdae	Arzneimittelkommission der deutschen Ärzteschaft
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
CCO	Cancer Care Ontario
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
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	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
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 [10]. Zusammenfassende Dokumentation Zusammenfassende Dokumentation Stand: 10. September 2013 über die Änderung der Arzneimittel-Richtlinie (AM-RL) Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Axitinib *siehe ergänzend auch:* **IQWiG, 2012 [13].** **Axitinib – Nutzenbewertung gemäß § 35a SGB V** (IQWiG-Berichte – Nr. 149)	**Fazit:** Zugelassenes Anwendungsgebiet von Axitinib (Inlyta®) gemäß Fachinformation1 (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**.
G-BA, 2009 [9]. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über die Einleitung eines Stellungnahmeverfahrens zur Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XI - Besondere Arzneimittel Besondere Arzneimittel nach § 73d SGB V bei der Behandlung des metastasierten und/oder fortgeschrittenen Nierenzellkarzinoms: Everolimus	**Fazit:** Everolimushaltige Arzneimittel werden als besondere Arzneimittel gemäß § 73d SGB V in Anlage XI aufgenommen, weil Sie die Kriterien des § 73d SGB V erfüllen. Bei Everolimus bezieht sich das Verfahren zur Verordnung besonderer Arzneimittel auf die Behandlung von Patienten mit fortgeschrittenem Nierenzellkarzinom, bei denen es während oder nach einer gegen VEGF gerichteten Therapie zu einer Krankheitsprogression kommt.

Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews in dem Anwendungsgebiet identifiziert.

Systematische Reviews

Coppin C et al., 2011 [7]. Targeted therapy for advanced renal cell carcinoma	1. Fragestellung To provide a systematic and regularly updated review of randomized studies testing targeted agents in advanced renal cell cancer. To identify the type and degree of clinical benefit of targeted agents over the prevailing standard of care
	2. Methodik ***Population:*** – Adults with metastatic or locally inoperable renal cell carcinoma, histologically verified at presentation or relapse. – Patients may or may not have received prior systemic therapy [FB-Med: Hier nur Ergebnisse von Studien dargestellt, in denen die Mehrzahl der Patienten vorbehandelt wurden] ***Intervention:*** – Agents with known or presumed molecular targets and known or presumed anti-angiogenesis agents – Classic immunotherapy agents, including recombinant cytokines and their predecessors, were excluded from this definition of targeted therapy, but may have been included as part of the regimen in any study arm. ***Komparator:*** – different dose and/or schedule of the same agent(s) – placebo or hormonal control – cytokine control (interferon-alfa) – targeted agent ***Endpunkte:*** – achievement of tumour shrinkage or disease stabilization according to commonly recognized criteria – overall survival or progression-free survival – quality-of-life outcomes – adverse events ***Suchzeitraum:*** January 2000 to June 2010. ***Anzahl eingeschlossene Studien/Patienten (Gesamt):***

	25 RCTs (n=7484) (=13 comparisons) ***Qualitätsbewertung der Studien:*** Cochrane Risk of Bias
	3. Ergebnisdarstellung – Risk of bias was low for studies that were placebo-controlled, had a primary outcome of overall survival, or that evaluated progression by independent radiologic reviewers unaware of the intervention allocation (siehe Anhang) *In Synopse nur Ergebnisse zum second-line treatment dargestellt:* **Everolimus** Following encouraging non-randomized studies in this setting, everolimus was compared to placebo in 410 heavily pretreated ambulatory patients with disease progression on or within 6 months of sunitinib and/or sorafenib. The primary endpoint of progression-free survival was improved from a median 1.9 months for placebo to 4.0 months for everolimus (HR = 0.30, P < 0.0001), with an associated 2- month delay in decline of performance status and no detriment to overall quality-of-life from toxicity. The probability of remaining progression-free at 10 months on study was 25% on everolimus versus < 2% for placebo. The remission rate was very low. The main concerns with this agent are reversible immunosuppression, non-infectious pneumonitis, and hyperglycemia. **Second-line targeted agent after VEGFR inhibitor failure** An increasingly relevant question is the value of second-line agents after initial targeted therapy. No identified studies address this question for patients receiving initial bevacizumab plus interferon. One large study enrolled patients progressing on or within six months of the oral VEGFR inhibitors sunitinib or sorafenib, comparing the oral mTOR inhibitor everolimus with placebo, the appropriate comparator in this setting. Patients were required to have renal cancers with a clear cell component but could also have received cytokine therapy. Median progression- free survival was prolonged from1.9 to 4months (HR 0.30), accompanied by delayed decline in performance status without adverse effect on quality-of-life. A survival benefit could not be demonstrated on an intent to-treat basis (problem of switching to everolismus arm); a final analysis of survival is awaited.
	4. Fazit der Autoren *1. Following initial interferon therapy, sorafenib improved quality of life*

	and delayed disease growth compared to placebo. *2. Following initial targeted therapy with sunitinib or sorafenib, daily oral everolimus delayed cancer growth compared to placebo but did not result in remissions or improve quality of life. Survival was similar but most placebo-assigned patients received everolimus later, making survival interpretation difficult.* *Several agents with specified molecular targets have demonstrated clinically useful benefits over interferon-alfa, and also after either prior cytokine or initial anti-angiogenesis therapy.*
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: keine näheren Angaben Intervention: combining or sequencing systemic targeted therapies Komparator: aktive Substanz oder Placebo Endpunkt: primary endpoints: PFS, OS, Secondary endpoints: harms of treatment Suchzeitraum (Aktualität der Recherche): the original EAU search was updated (covering the period from January 1, 2000, to September 30, 2013) methods protocol of the European Association of Urology (EAU) renal cell carcinoma 2013 guidelines was used as a basis for the search strategy Datenbanken: Medline, Medline In- Process, Embase, Cochrane Controlled Trials Register (Cochrane Library, Issue 8, 2013), and the Latin American and Caribbean Center on Health Sciences Information System. The search was complemented by additional sources including systematic reviews from the Cochrane Database of Systematic Reviews (Cochrane Library, Issue 8, 2013), recent conference proceedings of the American Society of Clinical Oncology and European Society of Medical Oncology, ongoing trials from clinicaltrials.gov and the World Health Organisation International Clinical Trials Registry Anzahl eingeschlossene Studien/Patienten (Gesamt): n=24 RCTs für qualitative Betrachtung, n=4 für quantitative Auswertung

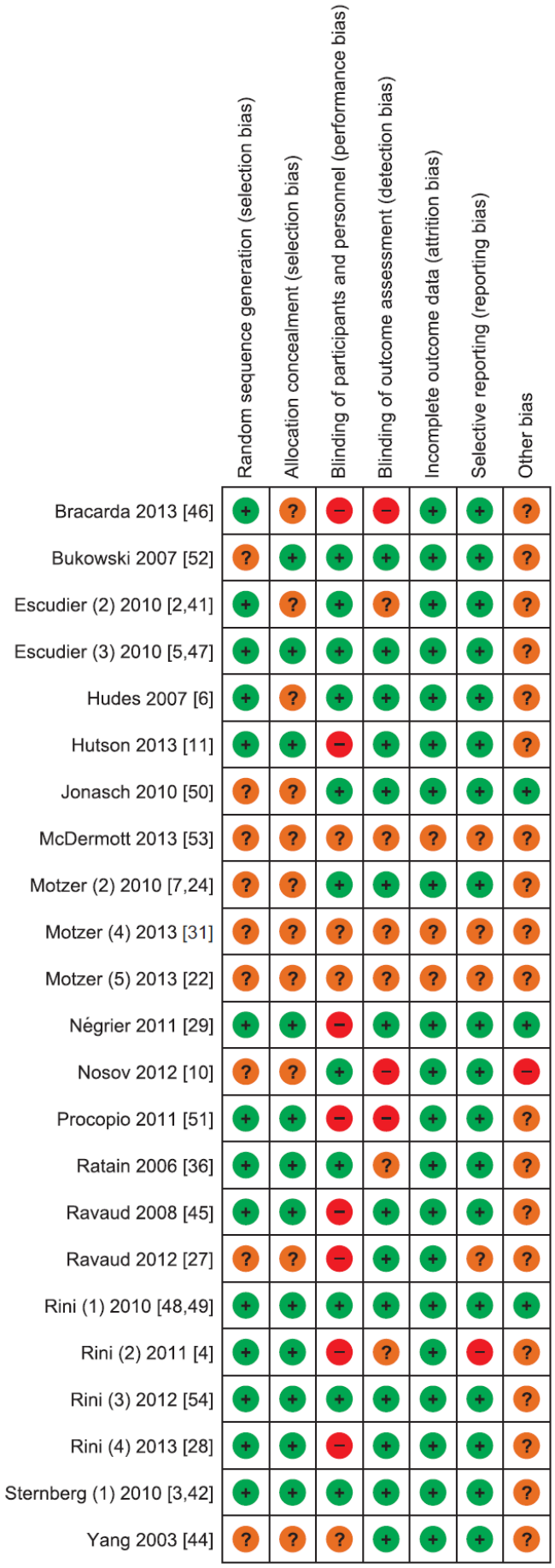
	Qualitätsbewertung der Studien: Cochrane risk of bias tool Hier sind die Ergebnisse der qualitativen Bewertung dargestellt
	3. Ergebnisdarstellung <u>post-VEGF/VEGFR inhibition setting</u> studies investigating sequencing beyond the first-line setting had broad inclusion criteria and no stratification based on prognostic criteria! RCTs support the use of both mTOR inhibitors and VEGFR inhibition in the VEGFR TKI–resistant setting. AXIS trial comparing two TKIs (axitinib vs. sorafenib) following first-line VEGF inhibition: difference in PFS was significant in the favour of axitinib versus sorafenib, the gain in PFS was short, and no difference in OS was detected in the final analysis. INTORSECT study: direct comparison between different classes of agents (temsirolimus, ie, an mTOR inhibitor, vs sorafenib, ie, a VEGFR TKI) following progression on sunitinib, but it failed to define an optimal sequence because there was no statistical significant difference in PFS. SWITCH-I trial investigating two sequential treatments (sorafenib/sunitinib vs sunitinib/sorafenib) found no significant difference in total PFS, OS, disease control rate, and first-line PFS between the two arms. RECORD-1 phase 3 RCT, designed to evaluate the mTOR inhibitor everolimus as second-line treatment versus placebo, have to be interpreted with caution because only 21% of the patients (53% received two previous treatments including one VEGFR inhibition plus cytokine) were purely second-line post sunitinib. **Kurzzusammenfassung der Studien siehe Table 1:**

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


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Bracarda 2013 [46]
Bukowski 2007 [52]
Escudier (2) 2010 [2,41]
Escudier (3) 2010 [5,47]
Hudes 2007 [6]
Hutson 2013 [11]
Jonasch 2010 [50]
McDermott 2013 [53]
Motzer (2) 2010 [7,24]
Motzer (4) 2013 [31]
Motzer (5) 2013 [22]
Négrier 2011 [29]
Nosov 2012 [10]
Procopio 2011 [51]
Ratain 2006 [36]
Ravaud 2008 [45]
Ravaud 2012 [27]
Rini (1) 2010 [48,49]
Rini (2) 2011 [4]
Rini (3) 2012 [54]
Rini (4) 2013 [28]
Sternberg (1) 2010 [3,42]
Yang 2003 [44]

	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
Poggiani C et al., 2012 [18]. Axitinib for the second-line treatment of metastatic renal cell carcinoma (mRCC) *sieher auch:* CADTH, 2013 [6]. Pan-Canadian Oncology Drug Review, Final Clinical Guidance Report: Axitinib (Inlyta) for metastatic Renal Cell Carcinoma ➔ Bewertung auf 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: 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 efficacy → AXIS Trial For safety 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). Subgroup analysis 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.

	Ergebnisse weiterer Studien zur Sicherheit (basierend auf → 2 single-arm, open-label phase II trials assessing the safety and efficacy of 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. 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*.
Heng DY et al., 2014 [11]. Comparative Effectiveness of Second-Line Targeted Therapies for Metastatic Renal Cell Carcinoma: A Systematic Review and Meta-Analysis of Real-World Observational Studies	1. Zielsetzung 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. Among these 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.

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.

Table 1. Studies comparing OS and PFS with VEGF TKI-mTORi versus VEGF TKI-VEGF TKI (HR<1 favors second-line mTORi versus 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]
Iacovelli et al. 2013	Medical records from multiple centers in Italy	Patients consecutively treated 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, pazopanib, 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 targeted therapy in 2010 or later	Everolimus and temsirolimus	Sunitinib, sorafenib, pazopanib, axitinib[e]	Y	Y	Y	138	79	N/A	0.74 (0.48, 1.15)

Estimated treatment effects of second-line mTORi versus VEGF TKI were synthesized for OS and PFS across all identified studies using meta-analysis. Treatment effects were measured as hazard ratios (HRs). Pooled HRs and associated 95% confidence intervals (CIs) and P values were estimated under a random effects model. Separate meta-analyses were then applied to the subgroup of adjusted,

	multicenter, retrospective cohort studies. When studies did not report HRs, they were imputed based on reported medians and associated 95% CIs for time to event and a constant hazard assumption. In each meta-analysis, heterogeneity was assessed using I^2 and tested with Cochran's Q statistic and its associated P value. Small study bias was also assessed using funnel plots and Egger's tests.
	3. Ergebnisdarstellung • OS (basierend auf 10 Studien): Significant heterogeneity in estimated second-line treatment effects (I^2=68%; P=0.001). Four of these were adjusted, multicenter, retrospective cohort studies, and these showed no evidence of heterogeneity (I^2=0%) and a significant association between secondline mTORi (>75% everolimus) and longer OS compared to VEGF TKI (>60% sorafenib, no axitinib) (HR=0.82, 95% CI: 0.68 - 0.98) in a meta-analysis. • PFS (basierend auf 7 Studien): Significant heterogeneity overall and among the adjusted, multicenter, retrospective cohort studies. Real-world observational data for axitinib outcomes was limited at the time of this study
	4. Fazit der Autoren: *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. Within the subset of adjusted, multicenter observational studies, second-line use of mTORi was associated with significantly prolonged survival compared with second-line use of VEGF TKI.* 5. Anmerkungen der Autoren: • Study designs differed substantially among the 10 studies reporting OS
Ibrahim EM et al., 2013 [12]. Sunitinib adverse events in metastatic renal cell carcinoma: a meta-analysis	1. Zielsetzung: 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. Heterogenität: Angabe I^2 Publikationsbias: Funnel Plot
	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).* 5. Anmerkungen FBMed: • Unter Vorbehandlung mit einer systemischen Therapie nicht klar wieviele davon eine VEGF Therapie darstellen.

Leitlinien

Benahmed N. et al., 2015 [4]. **Belgian Health Care Knowledge Centre (KCE)** Renal cancer in adults: diagnosis, treatment and follow-up	Belgian Health Care Knowledge Centre (KCE) – Diagnosis, staging, treatment and follow-up of patients with confirmed 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. – This guideline was developed as a result of a collaboration between multidisciplinary groups of practising clinicians and KCE experts. Guideline development and literature review expertise, support, and facilitation were provided by the KCE Expert Team. – The roles assigned to the GDG (Guideline Development Group) were: • To define the clinical questions, in close collaboration with the KCE Expert Team and stakeholders; • To identify critical and important outcomes; • To provide feedback on the selection of studies and identify further relevant manuscripts which may have been missed; • To provide feedback on the content of the guideline; • To provide judgement about indirectness of evidence; • To provide feedback on the draft recommendations; • To address additional concerns to be reported under a section on ‘other considerations’. – The CPG (Clinical Practice Guideline) addresses the following clinical topics: • Diagnosis and staging • Treatment of localised disease • Treatment of metastatic disease • Palliative care • Follow-up – 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. Recommendations from foreign guidelines were submitted to the GDG to validate their applicability in the Belgian context. If no high-quality, recent guidelines relevant to the research question are available, the general approach began with the search for systematic reviews. In addition to a search in OVID Medline, the National Guideline Clearinghouse and the GIN database were searched to identify relevant guidelines. – 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. – For the diagnostic questions, systematic reviews, diagnostic accuracy studies and RCTs were searched; for the other research questions, systematic reviews, RCTs or comparative observational studies (in the absence of RCTs) were searched. Only articles published in Dutch, English and French were included. – To be included a primary study had to: • be an RCT, an observational study or a diagnostic accuracy study; • address at least one of the research questions; • evaluate at least one of the selected (critical and important) outcomes. – 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. Based on an overall assessment, 3 high quality guidelines were selected with a general scope. We selected one supplementary guideline that was based on a well-documented systematic review of the literature that focused only on follow-up and that we used to formulate recommendations on that chapter. Selected (systematic) reviews were critically appraised using the AMSTAR checklist2. Retrieved diagnostic studies were assessed for the risk of bias by means of the QUADAS-2 tool. – The quality appraisal of RCTs for therapeutic interventions was

performed using the "Cochrane Collaboration's tool for assessing risk of bias". For each criterion the definitions described in the Cochrane Handbook were used. If applicable, risk of bias for the items regarding detection bias and attrition bias were assessed per class of outcomes (e.g. subjective and objective outcomes). At the end, each study was labelled as low risk of bias, unclear risk of bias or high risk of bias according to the criteria described in the Cochrane Handbook. Study limitations of observational studies were evaluated using a tool developed by KCE, for cohort studies and case control studies.

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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.

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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.

Treatment of local recurrence/ metastases

Local therapy of metastases in mRCC

Conclusion

Due to the lack of well-designed trial, no recommendation can be made over local therapy of metastases in mRCC.

Targeted therapy

Second-line treatment

Sorafenib can be considered as second-line treatment in clear cell metastatic renal cell carcinoma. (LoE High, Strength of Recommendation Strong)

Evidence

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DKG, 2015 [14]. **Deutsche Krebsgesell-schaft.** S3-Leitlinie Diagnostik, Therapie und Nachsorge des Nierenzellkarzi-noms	Fragestellung: *Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms* **Grundlage der Leitlinie** **Schlüsselfragen zur systemischen Therapie in der metastasierten Situation** • Welche Substanzen stehen in der second-line zu Verfügung? • Wie sind die Unterschiede in dieser Gruppe hinsichtlich des Überlebens und des Nebenwirkungsprofils? • Gibt es bereits empfohlene Sequenzen? • Gibt es Kombinationstherapien, die empfohlen werden können? **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 • restlichen Themen durch Dr. Loitsch in Zusammenarbeit mit den Arbeitsgruppenmitgliedern: Auswahl der Literatur durch Fachexperten • 3 Konsensuskonferenzen mit TED-Abstimmung, finale schriftliche Abstimmung • CoI dokumentiert und einsehbar • Suchstrategie veröffentlicht

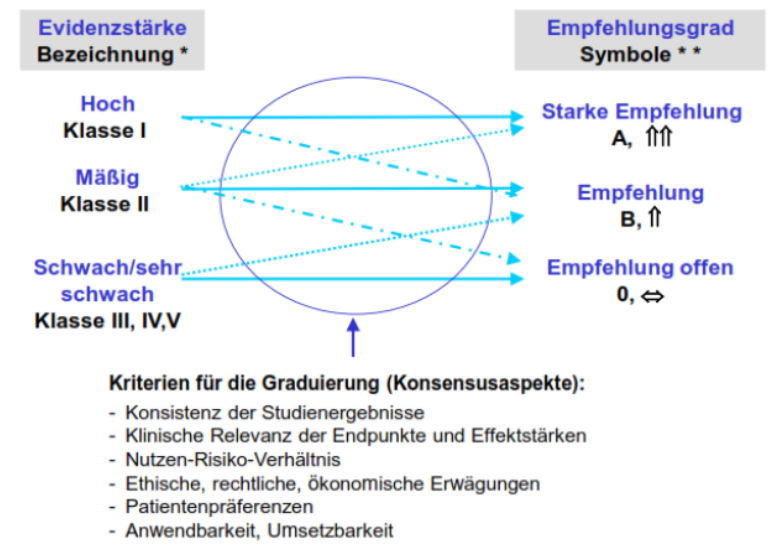
	• Evidenztabellen einsehbar  **Kriterien für die Graduierung (Konsensusaspekte):** - Konsistenz der Studienergebnisse - Klinische Relevanz der Endpunkte und Effektstärken - Nutzen-Risiko-Verhältnis - Ethische, rechtliche, ökonomische Erwägungen - Patientenpräferenzen - Anwendbarkeit, Umsetzbarkeit *: blau = Evidenzstärke nach GRADE bzgl. des gesamten ‚body of evidence', schwarz = Evidenzklassifikation bzgl. Einzelstudien, z.B. nach Oxford; **: Empfehlungsgraduierung im Programm für Nationale Versorgungsleitlinien. Die Empfehlungen werden nach Möglichkeit analog formuliert: Starke Empfehlung: „soll"; (abgeschwächte) Empfehlung: „sollte"; Negativ-Empfehlungen werden entweder rein sprachlich ausgedrückt („nicht" / „kann verzichtet werden") bei gleichen Symbolen oder sprachlich mit zusätzlich nach unten gerichteten Pfeilen; Offene Empfehlungen drücken eine Handlungsoption in Unsicherheit aus („kann erwogen werden" / „kann verzichtet werden"). Quelle: AWMF-Regelwerk, modifiziert **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

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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

Zielgerichtete Therapie des fortgeschrittenen und/oder metastasierten klarzelligen Nierenzellkarzinoms

7.5.2. Zweitlinientherapie

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

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:

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. **Palliative Radiotherapie** Bei Patienten mit Nierenzellkarzinom und Hirn-/Knochenmetastasen, spinaler Kompression und anderen symptomatischen Metastasen soll die Indikation für eine palliative Strahlentherapie geprüft werden. *(Empfehlungsgrad A, Level of Evidence 2, Starker Konsens)* Evidenzbasis Knochenmetastasen und spinale Kompression: 69. Tumoren, L.W.U., Renal cell carcinoma. Nation-wide guideline, Version: 2.0. 2010, Integraal Kankercentrum Nederland (IKNL): Utrecht.

	408. Hunter, G.K., et al., The efficacy of external beam radiotherapy and stereotactic body radiotherapy for painful spinal metastases from renal cell carcinoma. Pract Radiat Oncol, 2012. 2(4): p. e95-e100. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/24674192 483. Lutz, S., et al., Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. International Journal of Radiation Oncology* Biology* Physics, 2011. 79(4): p. 965-976. 484. Chow, E., et al., Update on the systematic review of palliative radiotherapy trials for bone metastases. Clin Oncol (R Coll Radiol), 2012. 24(2): p. 112-24. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/22130630 485. Lutz, S., The role of radiation therapy in controlling painful bone metastases. Curr Pain Headache Rep, 2012. 16(4): p. 300-6. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/22576786 486. Prewett, S. and R. Venkitaraman, Metastatic spinal cord compression: review of the evidence for a radiotherapy dose fractionation schedule. Clin Oncol (R Coll Radiol), 2010. 22(3): p. 222-30. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/20138487 487. Rades, D., et al., A new prognostic factor for the survival of patients with renal cell carcinoma developing metastatic spinal cord compression. Strahlenther Onkol, 2014. 190(7): p. 667-70. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/24535650 <u>Multiple Hirnmetastasen:</u> 69. Tumoren, L.W.U., Renal cell carcinoma. Nation-wide guideline, Version: 2.0. 2010, Integraal Kankercentrum Nederland (IKNL): Utrecht. 488. Fokas, E., et al., Radiotherapy for Brain Metastases from Renal Cell Cancer: Should Whole-Brain Radiotherapy Be Added to Stereotactic Radiosurgery? Strahlentherapie und Onkologie, 2010. 186(4): p. 210-217. 489. Dziggel, L., et al., A survival score for patients with brain metastases from less radiosensitive tumors treated with whole-brain radiotherapy alone. Strahlenther Onkol, 2014. 190(1): p. 54-8. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/23861153 490. Bennani, O., et al., Brain metastasis from renal cell carcinoma. Neurochirurgie, 2014. 60(1-2): p. 12-6. Wenn es ausschließlich um die Behandlung von lokalen Beschwerden geht, sollte eine palliative Radiotherapie (abhängig von der Ausbreitung/dem Ausmaß der Metastasierung und dem Allgemeinzustand des Patienten) durchgeführt werden. *(Empfehlungsgrad B, Level of Evidence 4, Konsens)* <u>Evidenzbasis</u> 69. Tumoren, L.W.U., Renal cell carcinoma. Nation-wide guideline, Version: 2.0. 2010, Integraal Kankercentrum Nederland (IKNL): Utrecht. 394. Kollender, Y., et al., Metastatic renal cell carcinoma of bone: indications and technique of surgical intervention. J Urol, 2000. 164(5): p. 1505-8. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/11025692 400. Jackson, R.J., S.C. Loh, and Z.L. Gokaslan, Metastatic renal cell carcinoma of the spine: surgical treatment and results. J Neurosurg, 2001. 94(1 Suppl): p. 18-24. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/11147860 491. DiBiase, S.J., et al., Palliative irradiation for focally symptomatic metastatic renal cell carcinoma: support for dose escalation based on a biological model. J Urol, 1997. 158(3 Pt 1): p. 746-9. 492. Huguenin, P.U., et al., Radiotherapy for metastatic carcinomas of the kidney or melanomas: an analysis using palliative end points. Int J Radiat Oncol Biol Phys, 1998. 41(2): p. 401-5. 493. Wilson, D., et al., The effect of biological effective dose on time to symptom progression in metastatic renal cell carcinoma. Clin Oncol (R Coll Radiol), 2003. 15(7): p. 400-7. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/14570088 494. Onufrey, V. and M. Mohiuddin, Radiation therapy in the treatment of metastatic renal cell carcinoma. Int J Radiat Oncol Biol Phys, 1985. 11(11): p. 2007-9. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/2414257 495. Halperin, E.C. and L. Harisiadis, The role of radiation therapy in the management of metastatic renal cell carcinoma. Cancer, 1983. 51(4): p. 614-7. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/6185207 496. Fossa, S.D., I. Kjolseth, and G. Lund, Radiotherapy of metastases from renal cancer. Eur Urol, 1982. 8(6): p. 340-2. 497. Pongracz, N., R. Zimmerman, and R. Kotz, Orthopaedic management of bony

metastases of renal cancer. Semin Surg Oncol, 1988. 4(2): p. 139-42.

Bei einer palliativen Bestrahlung von Patienten mit begrenzter Prognose sollten Kurzzeitkonzepte (z. B. 1 x 8 Gy oder 5 x 4 Gy) angewendet werden. Ist dahingegen von einem längeren Überleben (> 6 Monate) auszugehen, sollte ein Bestrahlungs-schema mit höherer Intensität und/oder Dosierung verwendet werden (z. B. 10 x 3 Gy). *(Empfehlungsgrad B, Level of Evidence 4, Konsens)*

Evidenzbasis
69. Tumoren, L.W.U., Renal cell carcinoma. Nation-wide guideline, Version: 2.0. 2010, Integraal Kankercentrum Nederland (IKNL): Utrecht.
498. Kjaer, M. and S.A. Engelholm, The clinical course and prognosis of patients with renal adenocarcinoma with solitary metastasis. Int J Radiat Oncol Biol Phys, 1982. 8(10): p. 1691-8.

Knochenmetastasen

Bei Frakturrisiko oder instabiler Fraktur sollte eine stabilisierende Chirurgie vor ei-ner Radiotherapie erwogen werden. *(Empfehlungsgrad B, Level of Evidence 4, Starker Konsens)*

Evidenzbasis
69. Tumoren, L.W.U., Renal cell carcinoma. Nation-wide guideline, Version: 2.0. 2010, Integraal Kankercentrum Nederland (IKNL): Utrecht.
402. Patchell, R.A., et al., Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet, 2005. 366(9486): p. 643-648. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/16112300

Spinale Kompression

Bei Patienten mit einer relativ günstigen Prognose und einer Myelonkompression infolge einer begrenzten Wirbelkörpermetastasierung (z. B. maximal 3 Wirbel, nicht spezifisch für das Nierenzellkarzinom) sollte einer chirurgischen Dekompression mit anschließender Radiotherapie (10 x 3 Gy) gegenüber einer alleinigen Radiothe-rapie der Vorzug gegeben werden. *(Empfehlungsgrad B, Level of Evidence 2, Starker Konsens)*

Evidenzbasis
69. Tumoren, L.W.U., Renal cell carcinoma. Nation-wide guideline, Version: 2.0. 2010, Integraal Kankercentrum Nederland (IKNL): Utrecht.
402. Patchell, R.A., et al., Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet, 2005. 366(9486): p. 643-648. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/16112300
408. Hunter, G.K., et al., The efficacy of external beam radiotherapy and stereotactic body radiotherapy for painful spinal metastases from renal cell carcinoma. Pract Radiat Oncol, 2012. 2(4): p. e95-e100. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/24674192
487. Rades, D., et al., A new prognostic factor for the survival of patients with renal cell carcinoma developing metastatic spinal cord compression. Strahlenther Onkol, 2014. 190(7): p. 667-70. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/24535650

Multiple Hirnmetastasen

Bei Patienten mit Nierenzellkarzinomen und multiplen (> 4

	Hirnmetastasen) und mäßigem bis gutem Karnofsky-Index wird eine Bestrahlung des gesamten Gehirns empfohlen. *(Empfehlungsgrad B, Level of Evidence 2, Starker Konsens)* Evidenzbasis 69. Tumoren, L.W.U., Renal cell carcinoma. Nation-wide guideline, Version: 2.0. 2010, Integraal Kankercentrum Nederland (IKNL): Utrecht. Es gibt Hinweise, dass bei Patienten mit > 4 Hirnmetastasen und einem Karnofsky-Performance-Index von mindestens 60-70 % durch die Ganzhirnbestrahlung weniger Metastasen-bedingte Beschwerden auftreten. *(Level of Evidence 3, Konsens)* Evidenzbasis 69. Tumoren, L.W.U., Renal cell carcinoma. Nation-wide guideline, Version: 2.0. 2010, Integraal Kankercentrum Nederland (IKNL): Utrecht. 416. Gaspar, L., et al., Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys, 1997. 37(4): p. 745-51. 421. Cannady, S.B., et al., Results of whole brain radiotherapy and recursive partitioning analysis in patients with brain metastases from renal cell carcinoma: a retrospective study. Int J Radiat Oncol Biol Phys, 2004. 58(1): p. 253-8. 503. Lagerwaard, F.J., et al., Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. Int J Radiat Oncol Biol Phys, 1999. 43(4): p. 795-803. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/10098435 Das mediane Überleben von unbehandelten Patienten mit Hirnmetastasen beträgt einen Monat, mit Kortikosteroiden 2 Monate und nach Behandlung mit WBRT 3-6 Monate. *(Level of Evidence 2, Konsens)* Evidenzbasis 69. Tumoren, L.W.U., Renal cell carcinoma. Nation-wide guideline, Version: 2.0. 2010, Integraal Kankercentrum Nederland (IKNL): Utrecht. 425. Noordijk, E.M., et al., The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. Int J Radiat Oncol Biol Phys, 1994. 29(4): p. 711-7. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/8040016 504. Schellinger, P.D., H.M. Meinck, and A. Thron, Diagnostic accuracy of MRI compared to CCT in patients with brain metastases. J Neurooncol, 1999. 44(3): p. 275-81.
Ljungberg B et al., 2015 [15]. Guidelines on Renal Cell Carcinoma	European Association of Urology (EAU) – →Diagnosis and treatment of RCC

	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

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

GoR modified from Oxford Centre for Evidence-based Medicine

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

Treatment of locally advanced RCC

Management of locally advanced unresectable RCC

In patients with non-resectable disease, embolisation can control symptoms, including gross haematuria or flank pain. The use of neoadjuvant targeted therapy to downsize tumours is experimental and cannot be recommended outside controlled clinical trials. [Hinweis: Keine Angabe LoE].

Evidence

222. Maxwell NJ, Saleem Amer N, Rogers E, et al. Renal artery embolization in the palliative treatment of renal carcinoma. Br J Radiol 2007 Feb;80(950):96-102. http://www.ncbi.nlm.nih.gov/pubmed/17495058
223. Hallscheidt P, Besharati S, Noeldge G, et al. Preoperative and palliative embolization of renal cell carcinomas: follow-up of 49 patients. Rofo 2006 Apr;178(4):391-9. http://www.ncbi.nlm.nih.gov/pubmed/16612730
224. Lamb GW, Bromwich EJ, Vasey P, et al. Management of renal masses in patients medically unsuitable for nephrectomy-natural history, complications and outcome. Urology 2004 Nov;64(5):909-13. http://www.ncbi.nlm.nih.gov/pubmed/15533476

Advanced/metastatic RCC

Local therapy of metastases in mRCC

Recommendations

No general recommendations can be made. The decision to resect metastases has to be taken for each site, and on a case-by-case basis; performance status, risk profiles, patient preference and alternative techniques to achieve local control, must be considered. (LoE: C)

In individual cases, stereotactic radiotherapy for bone metastases, and stereotactic radiosurgery for brain metastases can be offered for

	symptom relief. (LoE: C) Evidence 301. Dabestani S, et al. Local treatments for metastases of renal cell carcinoma: a systematic review. Lancet Oncol 2014 Nov;15(12):e549-61. http://www.ncbi.nlm.nih.gov/pubmed/25439697 302. Dabestani S, Hofmann F, Marconi L, et al; EAU Renal Cell Carcinoma Guideline Panel. Systematic review methodology for the EAU RCC Guideline 2013 update. http://www.uroweb.org/guidelines/online-guidelines/ 303. Alt AL, Boorjian SA, Lohse CM, et al. Survival after complete surgical resection of multiple metastases from renal cell carcinoma. Cancer 2011 Jul;117(13):2873-82. http://www.ncbi.nlm.nih.gov/pubmed/21692048 304. Brinkmann OA, Semik M, Gosherger G, et al. The role of residual tumor resection in patients with metastatic renal cell carcinoma and partial remission following immunotherapy. Eur Urol 2007;Suppl 6:641-5. 305. Kwak C, Park YH, Jeong CW, et al. Metastasectomy without systemic therapy in metastatic renal cell carcinoma: comparison with conservative treatment. Urol Int 2007;79(2):145-51. http://www.ncbi.nlm.nih.gov/pubmed/17851285 306. Lee SE, Kwak C, Byun SS, et al. Metastatectomy prior to immunochemotherapy for metastatic renal cell carcinoma. Urol Int 2006;76(3):256-63. http://www.ncbi.nlm.nih.gov/pubmed/16601390 307. Petralia G, Roscigno M, Zigeuner R, et al. Complete metastasectomy is an independent predictor of cancer-specific survival in patients with clinically metastatic renal cell carcinoma. Eur Urol Suppl 2010;9:162. 308. Russo P, Synder M, Vickers A, et al. Cytoreductive nephrectomy and nephrectomy/complete metastasectomy for metastatic renal cancer. ScientificWorldJournal 2007 Feb;7:768-78. http://www.ncbi.nlm.nih.gov/pubmed/17619759 309. Staehler M, Kruse J, Haseke N, et al. Metastasectomy significantly prolongs survival in patients with metastatic renal cancer. Eur Urol Suppl 2009;8:181. 310. Eggener SE, Yossepowitch O, Kundu S, et al. Risk score and metastasectomy independently impact prognosis of patients with recurrent renal cell carcinoma. J Urol 2008;180:873-8. http://www.ncbi.nlm.nih.gov/pubmed/18635225 311. Fuchs B, Trousdale RT, Rock MG. Solitary bony metastasis from renal cell carcinoma: significance of surgical treatment. Clin Orthop Relat Res 2005 Feb;(431):187-92. http://www.ncbi.nlm.nih.gov/pubmed/15685074 52 RENAL CELL CARCINOMA - UPDATE MARCH 2015 312. Hunter GK, Balagamwala EH, Koyfman SA, et al. The efficacy of external beam radiotherapy and stereotactic body radiotherapy for painful spinal metastases from renal cell carcinoma. Practical Radiation Oncology 2012;2:e95-e100. 313. Zelefsky MJ, Greco C, Motzer R, et al. Tumor control outcomes after hypofractionated and singledose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma. Int J Radiat Oncol Biol Phys 2012 Apr;82(5):1744-8. http://www.ncbi.nlm.nih.gov/pubmed/21596489 314. Fokas E, Henzel M, Hamm K, et al. Radiotherapy for brain metastases from renal cell cancer: should whole-brain radiotherapy be added to stereotactic radiosurgery?: analysis of 88 patients. Strahlenther Onkol 2010 Apr;186(4):210-7. http://www.ncbi.nlm.nih.gov/pubmed/20165820 315. Ikushima H, Tokuuye K, Sumi M, et al. Fractionated stereotactic radiotherapy of brain metastases from renal cell carcinoma. Int J Radiat Oncol Biol Phys 2000 Dec;48(5):1389-93. http://www.ncbi.nlm.nih.gov/pubmed/11121638 316. Staehler MD, Kruse J, Haseke N, et al. Liver resection for metastatic disease prolongs survival in renal cell carcinoma: 12-year results from a retrospective comparative analysis. World J Urol 2010 Aug;28(4):543-7. http://www.ncbi.nlm.nih.gov/pubmed/20440505 317. Amiraliev A, Pikin O, Alekseev B, et al. Treatment strategy in patients with pulmonary metastases of renal cell cancer. Interactive Cardiovascular and Thoracic Surgery 2012;15 (Suppl.):S20. 318. Zerbi A, Ortolano E, Balzano G, et al. Pancreatic metastasis from renal cell carcinoma: which patients benefit from surgical resection? Ann Surg Oncol 2008 Apr;15(4):1161-8. http://www.ncbi.nlm.nih.gov/pubmed/18196343 319. Kickuth R, Waldherr C, Hoppe H, et al. Interventional management of hypervascular osseous metastasis: role of embolotherapy before orthopedic tumor resection and bone stabilization. AJR Am J Roentgenol 2008 Dec;191(6):W240-7. http://www.ncbi.nlm.nih.gov/pubmed/19020210 320. Forauer AR, Kent E, Cwikiel W, et al. Selective palliative transcatheter embolization

of bony metastases from renal cell carcinoma. Acta Oncol 2007;46(7):1012-18. http://www.ncbi.nlm.nih.gov/pubmed/17851849

Systemic therapy for advanced/metastatic RCC

Targeted therapies

Recommendations

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-targeted therapy. (LoE: A)

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

Evidence

341. Escudier B, Eisen T, Stadler WM, et al; TARGET Study Group. Sorafenib in advanced clear-cell renal cell carcinoma. N Engl J Med 2007 Jan;356(2):125-34. http://www.ncbi.nlm.nih.gov/pubmed/17215530
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359. Motzer RJ, Escudier B, Oudard S, et al; RECORD-1 Study Group. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo controlled phase III trial. Lancet 2008 Aug;372(9637):449-56. http://www.ncbi.nlm.nih.gov/pubmed/18653228
360. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. Cancer 2010 Sept;116(18):4256-65. http://www.ncbi.nlm.nih.gov/pubmed/20549832
361. Calvo E, Escudier B, Motzer RJ, 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 Feb;48(3):333-9. http://www.ncbi.nlm.nih.gov/pubmed/22209391
362. Bracarda S, Hutson TE, Porta C, et al. Everolimus in metastatic renal cell carcinoma patients intolerant to previous VEGFr-TKI therapy: a RECORD-1 subgroup analysis. Br J Cancer 2012 Apr;106(9):1475-80. http://www.ncbi.nlm.nih.gov/pubmed/22441644

	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.

Bellmunt J et al., 2014 [3].

SEOM

SEOM clinical guidelines for the

Sociedad Española de Oncología Médica (SEOM)

– Diagnosis and treatment of renal cell carcinoma

Methodik

LoE and grades of recommendation (adapted from the Infectious Disease Society of America-United States Public Health Service Grading System)

treatment of renal cell carcinoma	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
	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 of metastatic non-clear cell histology

Some studies suggest now that patients with non-clear cell histology may benefit from treatment with sunitinib, sorafenib or temsirolimus [III, B]. The recent communication of ESPN trial (Tannir, N ASCO 2014) confirms that ev- erolimus is not considered today the first option for therapy and still the optimal therapy remains unclear and warrants further study [46]

Evidence
46. Vera-Badillo FE, Templeton AJ, Duran I, Ocana A, de Gouveia P, Aneja P, et al. Systemic therapy for non-clear cell renal cell carcinomas: a systematic review and meta-analysis. Eur Urol. 2014. doi:10.1016/j.eururo.2014.05.010.

Treatment algorithm

Treatment status	Setting	Category I evidence	Category II evidence
Treatment naive (ccRCC)	Good intermediate risk	Sunitinib Bevacizumab/ Interferon Pazopanib	Sorafenib High dose IL-2
	Poor risk	Temsirolimus	Sunitinib Sorafenib
Second-line (ccRCC)	Cytokine refractory	Sorafenib Pazopanib Sunitinib	
	TKI failure	Axitinib Everolimus Axitinib	Sorafenib
	Prior mTor inhibitors		Sunitinib
Non-Clear Cell histology			Temsirolimus Everolimus Sunitinib Sorafenib

Alberta Provincial Genitourinary Tumour Team, 2013 [1].

Alberta Health Services

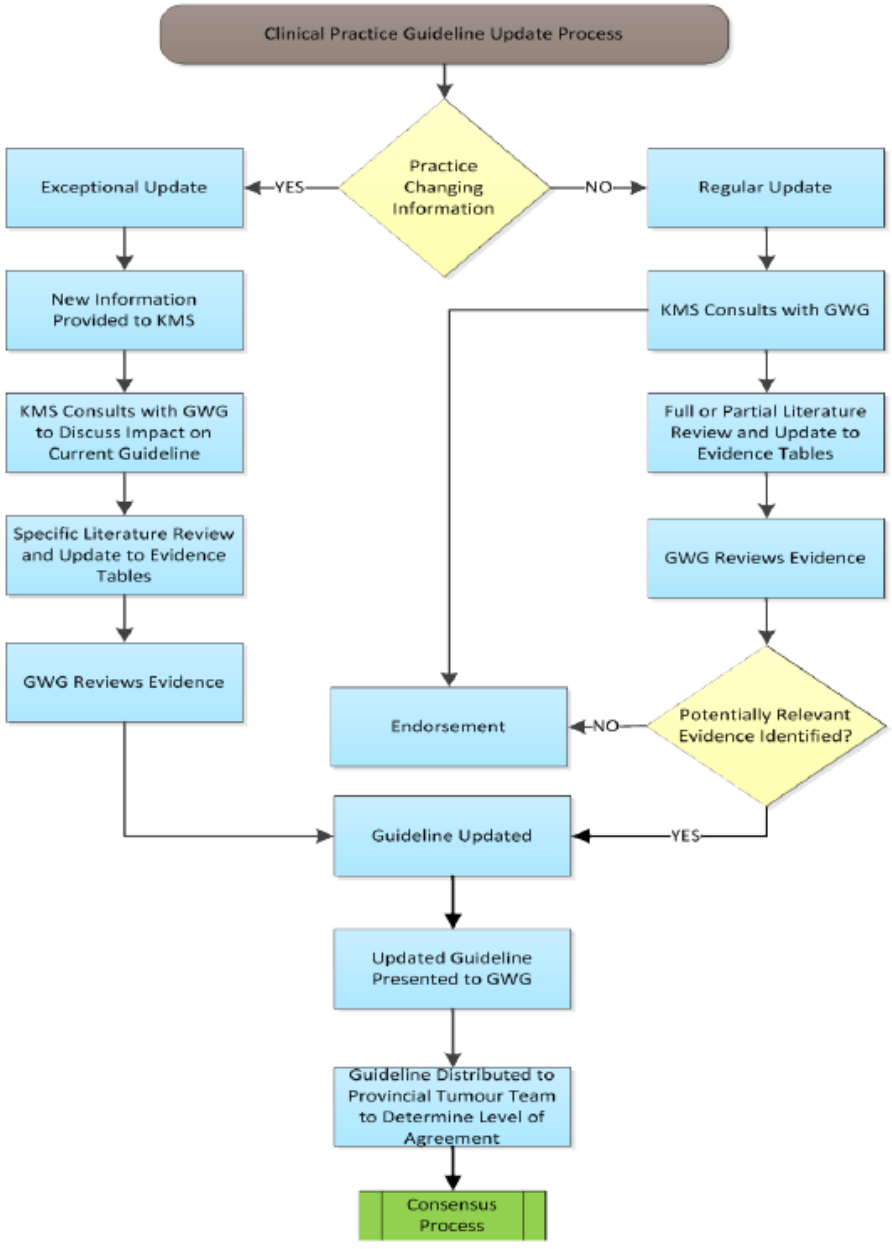
Guideline Question

- 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

Alberta Health Services Renal cell carcinoma	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

Guideline Update Process



Advanced Stage Disease

<u>Systematic Therapy</u>

For patients with advanced, node positive, and/or unresectable or metastatic disease, systemic is indicated.

	Second-line Therapy 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. Evidence 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.
	Methodik Grundlage der Leitlinie – The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (10). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by three members of the PEBC Genitourinary Cancer Disease Site Group (GU DSG) and one methodologist. – Update of version 2009 – The Evidence-Based Series Each EBS is comprised of three sections: • Section 1: Recommendations. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants. • Section 2: Evidentiary Base. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel. • Section 3: EBS Development Methods and External Review Process. Summarizes the guideline development process and the results of the formal external review of the draft version of Section 1: Recommendations and Section 2: Evidentiary Base.

	– External Review by Ontario Clinicians • The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners. – Literature Search Databases: 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 and the National Guidelines Clearing House were also searched for existing evidence-based practice guidelines. – Systematic Review with Meta-analyses In 2001, Coppin et al reported results of a Cochrane systematic review and meta-analysis. An update of this review was published in 2005. A third meta-analysis published in 1999 is not discussed here as the Cochrane review includes more recent data. – Randomized Controlled Trials Eight RCTs comparing IFN-α either alone or plus control therapy to control therapy alone published between 1988 and 2009 form the basis of this systematic review
	Recommendations 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. (See Related Guidelines EBS #3-8-4) 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. (See Related Guidelines EBS #3-8-2) <u>Evidence</u> PEBC Evidence-based Series: #3-8-2: Interleukin-2 in the Treatment of Patients with Unresectable or Metastatic Renal Cell Cancer. #3-8-3: The Role of Cytoreductive Nephrectomy in the Management of Patients Treated with Immunotherapy for Metastatic Renal Cell Cancer. #3-8-4: The Use of Inhibitors of Angiogenesis in Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer.

<table>
<tr><td>Dutch Dieticians Oncology Group, 2012 [8].

Renal cell carcinoma</td><td>Integraal kankercentrum Nederland (iKNL) / Urological Tumours National Working Group
– Renal cell carcinoma

Methodik

Grundlage der Leitlinie
– Update of the 2006 guideline and revision of the 2010 guideline
– Validity The period of validity of the guideline (maximum of 5 years) is being monitored by the VIKC programme office. For various reasons, it may be necessary to revise the guideline earlier than intended. The national working group Urological tumors will check the validity annually. Sections of the guideline will be amended in the interim, when required. At the latest, in 2014 a guideline working group will be installed to revise the guideline.
– Search in 2009
– 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'.

Treatment of local recurrence/metastases

Metastasectomy and radiotherapy

Recommendations:

Surgical decompression

No recommendations can be made in relation to surgical decompression for patients with renal cell carcinoma and spinal metastases on the basis of available literature. The guideline development group is of the opinion that a direct surgical decompression followed by radiotherapy may be considered for patients with renal cell carcinoma who are in a good condition with myelum compression as a result of solitary spinal metastasis.

Palliative radiotherapy

If it only concerns eradication of local complaints, it is recommended that radiotherapy be applied (dependent on the extent of the metastases and the condition of the patient).

Radiosurgery/stereotactic radiotherapy

It is recommended that a high dose of external irradiation or radiosurgery/stereotactic irradiation is applied in the case of solitary non-resectable metastases or solitary metastases that cannot be fully resected. The morbidity associated with surgery and/or radiotherapy should be discussed with the patient and any survival advantage weighed up for each individual patient.

Conclusions:

Surgical decompression

In the event of myelum compression as a result of limited vertebral metastasis (e.g. max. 3 vertebrae, not specifically the result of renal cell

carcinoma), there are indications that surgical decompression followed by radiotherapy (10 x 3 Gray) is preferable to radiotherapy only for selected patients with a relatively favourable prognosis. (Level 3: A)

Evidence

316 Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, Mohiuddin M, Young B. Direct decompressive surgical resection in the treatment of psinal cord compression caused by metastatic cancer: a randomised trial. Lancet. 2005 Aug. 20-26: 366 (9486):643-8

Palliative radiotherapy

It is plausible that painful bone metastases of a renal cell carcinoma may respond well to palliative radiotherapy or surgical resection with osteosynthetic stabilisation followed by postoperative radiotherapy. (Level 2 : B)

Evidence

80 DiBiase SJ, Valicenti RK, Schultz D, Xie Y, Gomella LG, Corn BW. Palliative irradiation for focally symptomatic metastatic renal cell carcinoma: Support for dose escalation based on a biological model. Journal of Urology 1997 Sep;158(3):746-9.
104 Fossa SD, Kjolseth I, Lund G. Radiotherapy of metastases from renal cancer. Eur.Urol. 1982;8(6):340-2.
138 Halperin EC, Harisiadis L. The role of radiation therapy in the management of metastatic renal cell carcinoma. Cancer 1983 Feb 15;51(4):614-7.
157 Huguenin PU, Kieser S, Glanzmann C, Capaul R, Lutolf UM. Radiotherapy for metastatic carcinomas of the kidney or melanomas: An analysis using palliative end points. International Journal of Radiation Oncology Biology Physics 1998 May;41(2):401-5.
164 Jackson RJ, Loh SC, Gokaslan ZL. Metastatic renal cell carcinoma of the spine: surgical treatment and results. J Neurosurg Spine 2001Jan; 94(1):18-24.
201 Kollender Y, Bickels J, Price WM, Kellar KL, Chen J, Merimsky O, Meller I, Malawer MM. Metastatic renal cell carcinoma of bone: indications and technique of surgical intervention. J Urol 2000 Nov;164(5):1505-8.
301 Onufrey V, Mohiuddin M. Radiation therapy in the treatment of metastatic renal cell carcinoma. Int.J.Radiat.Oncol.Biol.Phys. 1985 Nov;11(11):2007-9.
325 Pongracz N, Zimmermann R, Kotz R. Orthopaedic management of bony metastases of renal cancer. Semin Surg Oncol 1988:4(2):139-142.
416 Wilson D, Hiller L, Gray L, Grainger M, Stirling A, James N. The effect of biological effective dose on time to symptom progression in metastatic renal cell carcinoma. Clinical Oncology 2003;15(7):400-7.

In relation to palliative irradiation with a limited prognosis, it is the opinion of the guideline development group that a short irradiation series of 1 to 5 times is the treatment of choice (for example, 1x8 Gy or 5x4 Gy). In relation to palliative irradiation with a limited prognosis, it is the opinion of the guideline development group that a short irradiation series of 1 to 5 times is the treatment of choice (for example, 1x8 Gy or 5x4 Gy). (Level 4: opinion of the development group)

Stabilising surgery prior to the radiotherapy may be considered in the case of an instable fracture or risk of fracture. (Level 4: opinion of the development group)

Radiosurgery/stereotactic radiotherapy

There are indications that a solitary metastasis of a renal cell carcinoma, with a patient in a good overall condition (KS>70%), may be irradiated with a local higher dosis (for example: 13 x 3 Gy, 16 x 2.5 Gy) or by

means of radiosurgery/stereotactic radiotherapy. This applies to both bone and soft tissue metastases. (Level 3: C)

Evidence
193 Kjaer M, Frederiksen PL, Engelholm SA. Postoperative radiotherapy in stage II and III renal adenocarcinoma. A randomized trial by the Copenhagen Renal Cancer Study Group. Int.J.Radiat.Oncol.Biol.Phys. 1987 May;13(5):665-72.

Palliative radiotherapy for brain metastases

Recommendations:

Whole Brain Radiotherapy (WBRT)

In patients with renal cell carcinoma and multiple (>4) brain metastases and a reasonable to good Karnofsky performance status, irradiation of the entire brain (whole brain radiotherapy) is advised.

Radiosurgery/stereotactic radiotherapy

It is recommended that radiosurgery/stereotactic radiotherapy is administered to patients with a favourable risk profile (≤3 metastases, KS>70%, maximum diameter 3-3.5 cm, no progressive extracranial tumour activity), possibly supplemented with WBRT. The benefits and disadvantages of WBRT should be discussed with the individual patient.

Conclusions:

Whole Brain Radiotherapy (WBRT)

There are indications that total cranial irradiation leads to less complaints in patients with >4 brain metastases and a Karnofsky performance status of at least 60 to 70%. (Level 3: A2)

Evidence
116 Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys 2000 Jul 1;47(4):1001-6.
214 Lagerwaard FJ, Levendag PC, Nowak PJCM et al. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. Int J Radiat Oncol Biol Phys 1999; 43(4):795-803.
459 Cannady SB, Cavanaugh KA, Lee SY, Bukowski RM, Olencki TE, Stevens GH, et al. Results of whole brain radiotherapy and recursive partitioning analysis in patients with brain metastases from renal cell carcinoma: a retrospective study. Int J Radiat Oncol Biol Phys 2004 Jan 1;58(1):253-8.

The median survival of untreated patients is 1 month, with corticosteroids 2 months and after treatment with WBRT 3-6 months. Surgical extirpation of a solitary brain metastasis followed by WBRT, extends median survival to 6-12 months with select patients. Guideline Brain metastasis 2004: (Level 2)

Evidence
290 Noordijk EM, Vecht CT, Haaxma-Reiche H, Padberg GW, Voormolen JH, Hoekstra FH et al. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. Int J Radiat Oncol Biol Phys 1994 Jul 1;29(4):711-7.
588 Schellinger PD, Meinck HM, Thron A. Diagnostic accuracy of MRI compared to CCT in patients with brain metastasis. J Neurooncol 1999;44:275-81.

Radiosurgery/stereotactic radiotherapy

There are indications that radiosurgery/stereotactic radiotherapy cannot be given to select patients (≤3 metastases, KS >70%, maximum brain metastasis diameter 3-3.5 cm, no progressive extracranial tumour activity). (Level 3)

Evidence

500 Jensen RL, Shrieve AF, Samlowski W, Shrieve DC. Outcomes of patients with brain metastases from melanoma and renal cell carcinoma after primary stereotactic radiosurgery. Clin Neurosurg 2008;55:150-9:150-9.

527 Muacevic A, Kreth FW, Mack A, Tonn JC, Wowra B. Stereotactic radiosurgery without radiation therapy providing high local tumor control of multiple brain metastases from renal cell carcinoma. Minim Invasive Neurosurg 2004 Aug;47(4):203-8.

535 Noel G, Valery CA, Boisserie G, Cornu P, Hasboun D, Marc SJ, et al. LINAC radiosurgery for brain metastasis of renal cell carcinoma. Urol Oncol 2004 Jan;22(1):25-31.

The development group is of the opinion that surgery followed by radiotherapy may be considered in patients with a solitary brain metastasis (confirmed by MRI), no metastases elsewhere, a good general condition and a long disease-free interval, depending on the location. (Level 4: opinion of development group members)

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.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE, 2015 [16]. Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment	1.1 Axitinib is recommended as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine, only if the company provides axitinib with the discount agreed in the patient access scheme. *Reasoning* The Committee noted that the AXIS trial was well conducted and the relevant outcomes were assessed in line with the scope of the appraisal. However, it noted the difficulties in interpreting the AXIS trial results in this appraisal because of the lack of a best supportive care comparison. The Committee did not accept that axitinib was superior to sunitinib and pazopanib in the prior-cytokine population, and therefore did not accept that the end-of-life criteria had been met for this population, but it was aware that axitinib, sunitinib and pazopanib are used interchangeably in clinical practice. The Committee concluded that it was comparable to the alternative treatments recommended by NICE that meet the end-of-life criteria, and that there was now only a very small population included in the prior-cytokine group and more uncertainty could be accepted.
NICE, 2011 [17]. Everolimus for the second-line treatment of advanced renal cell carcinoma	1.1 Everolimus is not recommended for the second-line treatment of advanced renal cell carcinoma. 1.2 People currently receiving everolimus for the second-line treatment of advanced renal cell carcinoma should have the option to continue treatment until they and their clinician consider it appropriate to stop. Reasoning: The Committee agreed that the RECORD-1 trial was of good methodological quality and therefore the results could be considered robust. The Committee agreed that everolimus plus best supportive care had increased progression-free survival by approximately 3 months compared with placebo plus best supportive care. The Committee acknowledged that the relative estimates of overall survival according to the intention-to-treat analyses were biased because 81% of people had crossed over to receive everolimus in the trial. Therefore the Committee agreed that it was appropriate to adjust the results to control for the crossover using statistical modelling techniques. The Committee noted that the resulting estimates of overall survival were 16.2 and 16.1 months with everolimus plus best supportive care and 9.6 and 7.9 months with best supportive care using the IPCW and RPSFT methods, respectively. The ERG conducted exploratory analyses of the manufacturer's estimates derived using the RPSFT method (see section 3.25) and noted that the estimates of overall survival were 14.1 months with everolimus plus best supportive care and 8.9 months with best supportive care. The Committee therefore concluded that although there was sufficient evidence that everolimus increased progression-free and overall survival compared with best supportive care, the exact magnitude of the overall survival gain was uncertain because it was based on modelled data as opposed to data directly observed in the trial, but accepted that it would be more than 3 months.
Calvo E et al., 2013 [5]	Literaturrecherche bis 2011. Keine weiteren Methodischen Angaben wie z.B. Auswahl, Bewertung und Analyse der Literatur.

What is the optimal therapy for patients with metastatic renal cell carcinoma who progress on an initial VEGFr-TKI?	**<u>Wesentliche Informationen aus diesem Review:</u>** *Evidence-based guidelines for second-line therapy:* • Current clinical practice guidelines in the United States and Europe uniformly assign everolimus a grade A/category 1 recommendation for use in patients with mRCC who have failed initial VEGFr-TKI therapy, based on high-level clinical evidence from the randomized controlled phase III RECORD-1 (Renal Cell Cancer Treatment With Oral RAD001 Given Daily) trial. • Guidelines recently released by the National Comprehensive Cancer Network (NCCN) assign a category 1 recommendation to axitinb for use in patients with mRCC who failed previous systemic therapy,14 based on high-level evidence from the phase III AXIS [Axitinib as Second Line Therapy for Metastatic Renal Cell Cancer] trial. • Other therapies, including the VEGFr-TKIs sunitinib, sorafenib, and pazopanib and the VEGF inhibitor bevacizumab, have lower categories of evidence and consensus supporting their use as second-line therapies following failure of an initial VEGFr-TKI (sunitinib, category 2A; sorafenib, category 2A; bevacizumab, category 2B; and pazopanib, category 3). *Clinical efficacy after initial VEGFr-TKI failure* • <u>Second-line mTOR inhibitor therapy:</u> Second-line treatment with an mTOR inhibitor has been reported to provide median progression-free survival (PFS) or time to progression (TTP) ranging from 4.9 to 9.7 months in prospective studies and from 1.4 to 5.5 months in retrospective studies of patients with mRCC whose disease progressed after initial VEGFr-TKI therapy → basierend auf der phase III RECORD-1 trial of everolimus vs placebo in patients with mRCC who were previously treated with sunitinib and/or sorafenib (N = 416) • <u>Second-line VEGFr-TKI therapy:</u> Second-line treatment with a VEGFr-TKI has been reported to provide a median PFS or TTP ranging from 3.4 to 8 months in prospective studies and from 3.4 to 17.9 months in retrospective studies of patients with mRCC whose disease progressed after initial VEGFr-TKI therapy → wesentlich basierend auf → Results of prospective, multicenter, phase II studies evaluating treatment with a VEGFr-TKI after failure of initial VEGF-targeted therapy have demonstrated some efficacy & Phase III Results of the recent AXIS trial of sequential therapy suggest that the investigational VEGFr-TKI axitinib provides clinical benefit to patients with mRCC whose disease has progressed after initial treatment with a VEGFr-TKI. ➔ Derzeit keine direct vergleichenden Studien zu Zweitlinien VEGFr-TKI und mTOR inhibitor Therapie!

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**

#	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
3	cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*:ti,ab,kw
4	#2 and #3
5	hypernephroma* or rcc:ti,ab,kw
6	#1 or #4 or #5
7	#1 or #4 or #5 Publication Year from 2011 to 2016

SR, HTAs in Medline (PubMed) am 30.03.2016

#	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

#	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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