Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: Cabozantinib

Stand: Dezember 2016

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Cabozantinib **zur Behandlung des fortgeschrittenen Nierenzellkarzinoms nach vorangegangener zielgerichteter Therapie gegen VEGF**	
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 Überscht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*Nicht angezeigt.*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Axitinib: Beschluss über die Nutzenbewertung nach §35a SGB V vom 21.03.2013 Nivolumab: Beschluss über die Nutzenbewertung nach §35a SGB V vom 20.10.2016
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche.*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu prüfendes Arzneimittel:	
Cabozantinib L01XE26 CABOMETYX™	CABOMETYX ist indiziert für die Behandlung des fortgeschrittenen Nierenzellkarzinoms (renal cell carcinoma, RCC) bei Erwachsenen nach vorangegangener zielgerichteter Therapie gegen VEGF (vaskulärer endothelialer Wachstumsfaktor).
Tyrosin-Kinase-Inhibitoren (TKI)	
Sunitinib L01XE04 SUTENT®	Metastasierte Nierenzellkarzinome (mRCC) SUTENT wird bei Erwachsenen zur Behandlung fortgeschrittener/ metastasierter Nierenzellkarzinome (mRCC) eingesetzt.
Pazopanib L01XE11 Votrient®	Nierenzellkarzinom (RCC) Votrient ist angezeigt zur Erstlinien-Behandlung von erwachsenen Patienten mit fortgeschrittenem Nierenzellkarzinom und zur Behandlung von Patienten, die vorher eine Therapie ihrer fortgeschrittenen Erkrankung mit Zytokinen erhalten hatten.
Sorafenib L01XE05 Nexavar®	Nexavar ist angezeigt zur Behandlung von Patienten mit fortgeschrittenem Nierenzellkarzinom, bei denen eine vorherige Interferon-alpha- oder Interleukin-2-basierte Therapie versagt hat oder die für solch eine Therapie nicht geeignet sind.
Lenvatinib L01XE29 Kisplyx®	Kisplyx ist indiziert in Kombination mit Everolimus zur Behandlung von erwachsenen Patienten mit fortgeschrittenem Nierenzellkarzinom (renal cell carcinoma, RCC) nach einer vorhergehenden, gegen den vaskulären endothelialen Wachstumsfaktor (VEGF) gerichteten Behandlung.
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.
Immun-Checkpoint-Inhibitoren	
Nivolumab L01XC17 Opdivo®	Nierenzellkarzinom (RCC) OPDIVO ist als Monotherapie bei Erwachsenen zur Behandlung des fortgeschrittenen Nierenzellkarzinoms nach Vortherapie indiziert.
mTOR-Inhibitoren	
Everolimus L01XE10 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.

Zytokine	
Interferon alfa-2a L03AB04 Roferon®-A	Roferon-A wird für die Behandlung der folgenden Erkrankungen angewendet: - Fortgeschrittenes Nierenzell-Karzinom.
Aldesleukin L03AC01 PROLEUKIN® S	Zur Behandlung des metastasierten Nierenzellkarzinoms. Risikofaktoren, die zu reduziertem Ansprechen und mittlerem Überleben führen, sind: – Ein reduzierter Allgemeinzustand von ECOG 1 oder mehr – Metastatischer Befall in mehr als einem Organ – Ein Intervall von weniger als 24 Monaten zwischen Primärdiagnose und Ansetzen der Proleukin-S-Therapie. Ansprechraten und mittlere Überlebenszeit werden mit zunehmender Anzahl vorhandener Risikofaktoren geringer. Patienten mit allen drei Risikofaktoren sollten nicht mit Proleukin S behandelt werden.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

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

Inhalt

Indikation für die Synopse:

Fortgeschrittenes Nierenzellkarzinom nach vorangegangener Therapie.

Berücksichtigte Wirkstoffe/Therapien:

siehe: Übersicht 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 Nierenzellkarzinom durchgeführt. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw.

Internetseiten folgender Organisationen gesucht: CCO, ESMO, NCCN, NCI. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche wurde am 30.03.2016 beendet (Suchzeitraum eingeschränkt auf die letzten 5 Jahre) und ergab 942 Quellen. Eine Folgerecherche, die am 17.11.2016 beendet wurde (Suchzeitraum eingeschränkt auf 31.03.2016 bis 17.11.2016), ergab 178 Quellen. Die Treffer wurden in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Für die Synopse wurden nur die Quellen aus den letzten 5 Jahren berücksichtigt. Insgesamt ergab dies 15 Dokumente, 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, 2016 [5]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Nivolumab (neues Anwendungsgebiet) *siehe ergänzend auch:* **IQWiG, 2016 [9,10].** **Nivolumab (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V** (IQWiG-Berichte – Nr. 415)	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 04.04.2016):** Nierenzellkarzinom (RCC) OPDIVO ist als Monotherapie bei Erwachsenen zur Behandlung des fortgeschrittenen Nierenzellkarzinoms nach Vortherapie indiziert. **1) Patienten nach antiangiogenetischer Vortherapie** Zweckmäßige Vergleichstherapie: Everolimus Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Everolimus: Hinweis auf einen beträchtlichen Zusatznutzen. **2) Patienten nach Vortherapie mit Temsirolimus** Zweckmäßige Vergleichstherapie: Sunitinib Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Sunitinib: Ein Zusatznutzen ist nicht belegt**.**
G-BA, 2013 [7]. 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 [8].** **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 [6].	**Fazit:**

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	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

Coppin C et al., 2011 [3]. Targeted therapy for advanced renal cell cancer (RCC): a Cochrane systematic review of published randomised trials	**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 <u>Population:</u> – 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] <u>Intervention:</u> – 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. <u>Komparator:</u> – different dose and/or schedule of the same agent(s) – placebo or hormonal control – cytokine control (interferon-alfa) – targeted agent <u>Endpunkte:</u> – achievement of tumour shrinkage or disease stabilization according to commonly recognized criteria – overall survival or progression-free survival – quality-of-life outcomes – adverse events <u>Suchzeitraum:</u> January 2000 to June 2010. <u>Anzahl eingeschlossene Studien/Patienten (Gesamt):</u> 28eligible trials were identified, 26 RCTs (n=8603) <u>Qualitätsbewertung der Studien:</u> Cochrane Risk of Bias

	3. Ergebnisdarstellung *In Synopse nur Ergebnisse zum second-line treatment dargestellt:* Pazopanib The study of pazopanib 800 mg daily vs placebo (2:1 randomisation) included 202 patients after prior cytokine…The primary outcome of PFS was significantly improved in both cytokine-pretreated and treatment-naïve patients (all patients median PFS 9.2 vs 4.2 months, HR 0.46; cytokine-pretreated HR 0.54, and treatmentna ï ve patients HR 0.40; all P < 0.001, overlapping 95%CIs). OS was similar for pazopanib-assigned and placebo-assigned patients (median OS 22.9 vs 20.5 months, HR 0.91, P = 0.22) but 54% of the latter received pazopanib after progression. Axitinib Axitinib is the most recently reported active oral VEGFR inhibitor from the second-line phase III AXIS study (FB Med: vs. Sorafenib) of 723 patients who had received one prior agent reflecting the range of current choices for first-line therapy (sunitinib 54%, cytokine 35%, other 11%)...PFS was significantly better for axitinib than sorafenib regardless of prior treatment (median PFS for all patients was 6.7 vs 4.7 months, HR 0.67, P < 0.001; HR 0.74 after prior sunitinib, HR 0.46 after cytokine). AE: Axitinib had more all-grade hypertension (40 vs 29%) and hypothyroidism (19 vs 8%) than sorafenib, considered on-target effects and consistent with axitinib having more selective action against VEGFRs. Axitinib also had more fatigue and dysphonia but less hand-foot syndrome, rash, and alopecia. Everolimus RECORD-1 compared everolimus 10 mg daily with placebo in 410 patients with progressive disease ≤ 6 months of sunitinib and/or sorafenib treatment. The primary endpoint of PFS by independent central review was improved (median PFS 4.9 vs 1.9 months, HR 0.33, P < 0.001). **Second-line targeted agent after VEGFR inhibitor failure** After first-line cytokine: based on preliminary data, axitinib may be superior to sorafenib. Pazopanib is an available alternative. After first-line sunitinib: everolimus; axitinib appears to have a higher response rate. After first-line sorafenib: everolimus yields prolonged PFS, but few objective responses, and unchanged overall HRQL. After first-line temsirolimus or BEV + IFN-α : no trials available. Referenzen 13. Escudier B , Eisen T , Stadler WM et al .Sorafenib for treatment of renal cell carcinoma: fi nal effi cacy and safety results of the phase III Treatment Approaches in

	Renal cancer Global Evaluation Trial . J Clin Oncol 2009 ; 27 :3312 – 8. 21. Sternberg CN , Davis ID , Mardiak J et al . Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial . J Clin Oncol 2010 ; 28 : 1061 – 8. 23. Rini BI , Escudier B , Tomczak P et al .Axitinib versus sorafenib as second-line therapy for metastatic renal cell carcinoma: results of phase III AXIS trial. J Clin Oncol 2011 ; 29 (Suppl.); abstract 4503 26. Motzer RJ , Escudier B , Oudard S et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomized, placebo-controlled phase III trial . Lancet 2008 ; 372 : 449 – 56
	4. Fazit der Autoren *Several trials examined agents in the second-line setting. After cytokine therapy, sorafenib (one study) and pazopanib (one study) prolonged PFS over placebo. A preliminary report of the investigational VEGF receptor inhibitor axitinib gave superior PFS to sorafenib after either prior cytokine or prior sunitinib treatment. After cancer progression ≤ 6 months of sunitinib and/or sorafenib therapy, everolimus prolonged PFS.* FB Med: direkter Vergleich nur für Axitinib vs. Sorafenib.

Systematische Reviews

Albiges L et al., 2015 [1]. **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, Suchzeitraum: 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 (n= 9589 Patienten) für qualitative Betrachtung, n=4 für metaanalytische Auswertung Qualitätsbewertung der Studien: Cochrane risk of bias tool
	3. Ergebnisdarstellung RoB: There were generally low risks of bias across studies; however, clinical and methodological heterogeneity prevented pooling of data for most studies. Cytokine pretreated patients Sequencing targeted therapy as second-line treatment in cytokine pretreated patients has been assessed in randomized phase 2 (sunitinib) and large phase 3 RCTs for sorafenib, pazopanib, and axitinib. The average PFS in these reports was approximately 8 mo in cytokine-refractory patients. Sunitinib, or other VEGF/VEGFR inhibiting therapies, have widely become the

	standard of care in the first-line setting. post-VEGF/VEGFR inhibition setting 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 is the only RCT 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. 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.

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

Leitlinien

NCCN, 2016 [15]. **Clinical Practice Guidelines in Oncology (NCCN Guidelines®)** Kidney Cancer. Version 02.2017	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology
	Methodik <u>Grundlage der Leitlinie</u> • Update der LL-Version von 1.2017 • Suchzeitraum: 07/15/15 until 07/15/16 in PubMed LoE / GoR The level of evidence depends upon the following factors, which are considered during the deliberation process by the Panel: - Extent of data (e.g., number of trials, size of trials, clinical observations only), - Consistency of data (e.g., similar or conflicting results across available studies or observations), and - Quality of data based on trial design and how the results/observations were derived (e.g., RCTs, non-RCTs, meta-analyses or systematic reviews, clinical case reports, case series). **NCCN Categories of Evidence and Consensus** **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. **All recommendations are category 2A unless otherwise noted.** For the ‘uniform NCCN consensus’ defined in Category 1 and Category 2A, a majority Panel vote of at least 85% is required.
	Empfehlungen Siehe Anhang Abbildung 1 und Abbildung 2.

Targeted Therapy

Targeted therapy utilizing tyrosine kinase inhibitors (TKIs) and anti-VEGF antibodies is widely used in first- and second-line treatments. To date, seven such agents have been approved by the FDA for the treatment of advanced RCC: sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, everolimus, and bevacizumab in combination with interferon.

Subsequent Therapy for Patients with Predominantly Clear Cell Carcinoma

Cabozantinib

with everolimus). The longer PFS and increased OS with cabozantinib when compared to everolimus makes cabozantinib a preferred choice in the second-line setting for advanced RCC.

Based on the METEOR trial results,[131,132] the NCCN Panel has included cabozantinib as a category 1 preferred subsequent therapy option.

Referenzen

131. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015;373:1814-1823. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26406150.

132. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol 2016;17:917-927. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27279544.

Nivolumab

Based on the results of the CheckMate 025[133] trial demonstrating superior OS with nivolumab compared with everolimus, the NCCN Panel has included nivolumab as a category 1, preferred subsequent therapy option

Referenzen

133. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015;373:1803-1813. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26406148.

Lenvatinib

Lenvatinib plus everolimus is listed as a category 1 recommendation for subsequent therapy by the NCCN Kidney Cancer Panel.

Referenzen

137. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26482279.

138. Motzer RJ, Hutson TE, Ren M, et al. Independent assessment of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma. Lancet Oncol 2016;17:e4-5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26758760.

Axitinib

Axitinib is listed as a category 1 recommendation as a subsequent therapy option by the NCCN Kidney Cancer Panel.

Referenzen

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Everolimus

Everolimus is listed as a category 2A subsequent therapy option in the NCCN Guidelines. It is important to note that two recent randomized phase III trials (discussed in sections above) compared the efficacy of everolimus with nivolumab and cabozantinib. The results of the CheckMate 025[133] trial demonstrated superior OS with nivolumab compared with everolimus. The METEOR trial[131] demonstrated longer PFS and OS with cabozantinib when compared to everolimus. Based on the results of these two phase III trials, eligible patients should preferentially receive either nivolumab or cabozantinib over everolimus.

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Sorafenib

progressed on prior cytokine therapy. Sorafenib has also been studied as second-line therapy in patients treated with sunitinib or bevacizumab and has been found to be safe, feasible, and effective.[147,148] Sorafenib is listed as a category 2A subsequent therapy option.

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Sunitinib

one agent over another.[150-154] Sunitinib is considered a category 2A subsequent therapy option.

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Pazopanib

Based on the above data, the NCCN Kidney Cancer Panel considers pazopanib a category 2A subsequent therapy option.

Referenzen

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Ljungberg B, 2016 [14]. **European Association of Urology (EAU)** Guidelines on renal cell carcinoma.	The European Association of Urology (EAU) Renal Cell Cancer (RCC)
	Methodik Grundlage der Leitlinie • Update of the 2015 publication • Suchzeitraum: 1st January 2013 to 30th July 2015 • The search was limited to studies representing high levels of evidence only (i.e. systematic reviews (SRs) with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies only) published in the English language. LoE / GoR References used in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence. [1]
	Empfehlungen Systemic therapy for advanced/metastatic RCC *Summary of evidence and recommendations for immunotherapy in*

[1] http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/

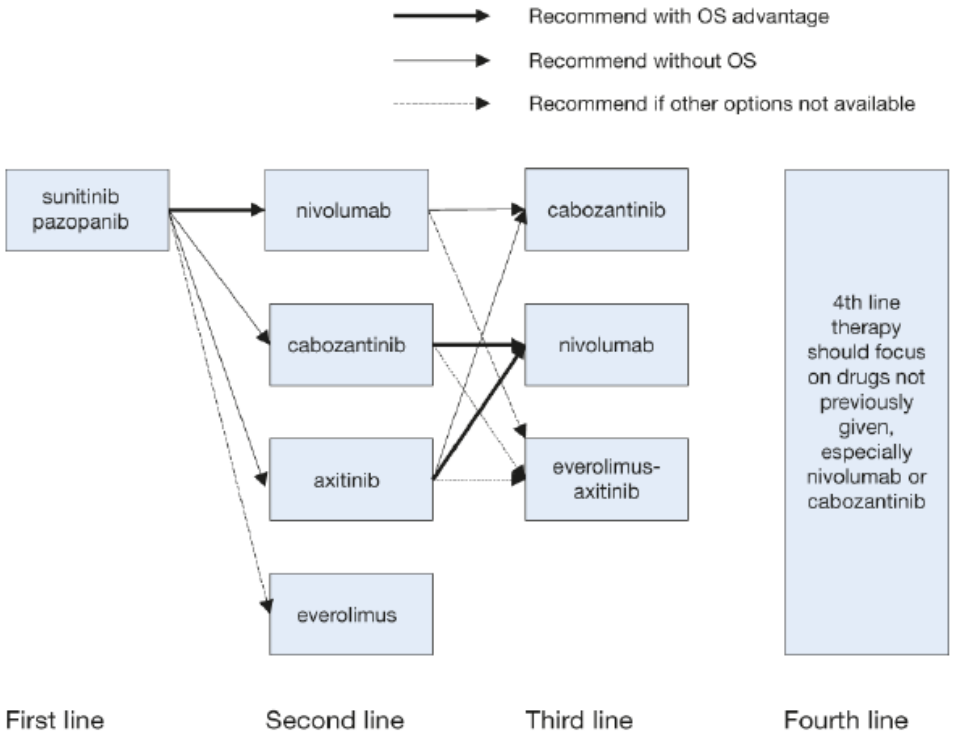
mRCC

Summary of evidence	LE
intermediate-risk tumours.	
Vaccination therapy with tumour antigen 5T4 showed no survival benefit over first-line standard therapy.	1b
Cytokine combinations, with or without additional chemotherapy, do not improve OS compared with monotherapy.	1b
Nivolumab leads to superior OS compared to everolimus in patients failing one or two lines of VEGF-targeted therapy.	1b

Recommendations	GR
Nivolumab is strongly recommended after one or two lines of VEGF-targeted therapy in metastatic RCC.	A
Monotherapy with IFN-α or HD bolus IL-2 is not routinely recommended as first-line therapy in metastatic RCC.	A

HD=high-dose; IL=interleukin; INF=interferon; OS=overall survival; PFS=progression-free survival; PS=performance status; VEGF=vascular endothelial growth factor.

Recommendations for patients with metastatic ccRCC who have failed one or more lines of VEGF targeted therapy



Siehe auch Anhang, Abbildung 3.

7.4.6.3.Summary of evidence and recommendations for systemic therapy in mRCC

Summary of evidence	LE
VEGF TKIs increase PFS and/or OS as both first-line and second-line treatments for clear-cell mRCC.	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.	1b
Sunitinib is more effective than IFN-α in treatment-naïve patients.	1b
Bevacizumab plus IFN-α is more effective than IFN-α in treatment-naïve low-risk and intermediate-risk patients.	1b
Pazopanib is superior to placebo in both naïve mRCC patients and post-cytokine patients.	1b
Pazopanib is not inferior to sunitinib in clear-cell mRCC patients.	1b
Temsirolimus monotherapy prolongs OS compared to IFN-α in poor-risk mRCC.	1b
Nivolumab is superior to everolimus in terms of OS and adverse events in patients failing one or two lines of VEGF-targeted therapy.	1b
Cabozantinib is superior to everolimus in terms of PFS in patients failing one or more lines of VEGF-targeted therapy.	1b
Everolimus prolongs PFS in patients who have previously failed or are intolerant of VEGF-targeted therapy.	1b
Sorafenib has broad activity in a spectrum of settings in clear-cell renal cancer patients previously treated with cytokine or targeted therapies. It is inferior to axitinib in both sunitinib or cytokine pre-treated patients.	4
Both mTOR inhibitors (everolimus and temsirolimus) and VEFG-targeted therapies (sunitinib or sorafenib) can be used in non-clear cell RCC.	3
No combination has proven to be better than single-agent therapy.	1a

Benahmed N et al., 2015 [2].

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.
- Search period for guidelines: ≥ 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
- 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. 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".

LoE

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

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

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

Table 2 – Levels of evidence according to the GRADE system

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

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

GoR

The strength of each recommendation was assigned using the GRADE system.

Table 4 – Strength of recommendations according to the GRADE system

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

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

Table 5 – Factors that influence the strength of a recommendation

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

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

Empfehlungen

<u>Second-line Treatment</u>

Conclusion

- Sorafenib improves PFS and CBR in comparison with placebo in low or intermediate risk mRCC patients. This advantage is also observed in sub-population such as elderly, prior cytokine treated patients. In addition, HRQoL is better rated by CC mRCC patients treated with sorafenib than by those treated with placebo whatever the patients' age (< 70 years vs ≥ 70 years).
- After cytokine treatment or in naïve patients, PFS, response rate are improved in CC mRCC patients treated with pazopanib in comparison to those treated with placebo. However, OS and HRQoL are not improved with this TKI.
- After one prior chemotherapy or immune/hormonal therapy, Cediranib improves PFS, partial response rate, stable disease rate or tumour size in mRCC patients in comparison with placebo.

- After systemic treatment other than VEGF pathway targeted therapy, Tivozanib improves PFS in mRCC patients in comparison with placebo.
- After immunotherapy, chemotherapy or hormonal therapy, improvement by Tivozanib in PFS in mRCC patients in comparison with sorafenib is not statistically significant. Only pooled results (naïve and previous therapy) were reported for OS, ORR and HRQoL.
- After VEGF-pathway therapy (sunitinib, sorafenib or both), IFN, IL-2, chemotherapy or bevacizumab, Everolimus improves PFS in mRCC patients in comparison with placebo. This advantage is maintained in elderly and in patients previously intolerant to sorafenib. However, it is not the case for patients previously intolerant to sunitinib. In addition, Everolimus does not improve OS in CC mRCC patients.
- After previous treatment with sunitinib, bevacizumab plus IFN-α, temsirolimus or cytokine, Axitinib improved PFS in comparison with Sorafenib in CC mRCC but no statistically significant difference in OS and QoL is observed.
- After sunitinib, Temsirolimus does not improve PFS, OS or ORR in mRCC patients in comparison with sorafenib.
- After cytokine treatment, there are no statistically significant difference in PFS and OS in patients treated with lapatinib orhormones.

Recommendations	Strength of Recommendation	Level of Evidence
• Sorafenib can be considered as second-line treatment in clear cell metastatic renal cell carcinoma.	Strong	High
• Pazopanib, sunitinib or sorafenib can be considered in metastatic renal cell carcinoma patients previously treated with cytokines *(IFN-α, IL-2)*.	Strong	Low
• Everolimus can be considered in metastatic renal cell carcinoma patients previously treated with Vascular endothelial growth factor (VEGF)-pathway targeted therapy *(i.e. bevacizumab, sunitib, sorafenib,…)* or cytokines *(IFN-α, IL-2)*.	Strong	Low
• Axitinib is recommended in metastatic renal cell carcinoma patients previously treated with VEGF-pathway targeted therapy or cytokines. *Note: Axitinib is reimbursed after a failure of first line treatment with TKI or cytokine.*	Strong	Low

Referenzen

Sorafenib:

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Leitlinienpro-gramm Onkologie, 2015	Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF), Deutschen Krebsgesellschaft e.V. (DKG) und Deutschen Krebshilfe (DKH); Federführende Fachgesellschaften: DGU, DGHO

[12].

S3-Leitlinie Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms

Version 1.0 – 09.2015

sowie

Leitlinienprogramm Onkologie, 2015 [13].

Leitlinienreport S3-Leitlinie Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms

Version 1.0 – 09.2015

Methodik

Grundlage der Leitlinie[2]

- Für die Erstellung der Leitlinie wurden zunächst durch die Leitliniengruppe prioritäre Fragestellungen definiert, relevante Fragestellungen gesammelt und beim Kick-off-Treffen der Leitliniengruppe am 29.10.2012 konkretisiert und konsentiert.
- Leitlinienadaption: Die Suche nach publizierten Leitlinien zu Diagnostik und Therapie des Nierenzellkarzinoms wurde im August 2012 durchgeführt und mittels DELBI Auswahl getroffen
- Diagnostik, direkter Vergleich systemischer Therapien wurde durch das Department für Evidenzbasierte Medizin und Klinische Epidemiologie der Donau-Universität Krems durchgeführt und Literaturstellen ausgewählt und mittels GRADE-Methodik bewertet
- 3 Konsensuskonferenzen mit TED-Abstimmung, finale schriftliche Abstimmung

Literaturrecherche: Januar 2013, Systematische Aktualisierungsrecherche mit Pubmed für den Zeitraum von Januar 2013 bis Januar 2014, durchgeführt am 26.01.2014

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

[2] Leitlinienreport S3-Leitlinie Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms: http://leitlinienprogramm-onkologie.de/uploads/tx_sbdownloader/LL_Nierenzell_LLReport_1.0.pdf

GoR

Tabelle 4: Schema der Empfehlungsgraduierung

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

Tabelle 5: Konsensusstärke

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

2.2.3. Statements

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

2.2.4. Expertenkonsens (EK)

Statements/Empfehlungen, für die eine Bearbeitung auf der Grundlage von Experten-konsens (es erfolgt keine systematische Recherche) der Leitliniengruppe beschlossen wurde, sind als „Expertenkonsens“ ausgewiesen. Für die Graduierung der Empfehlungen 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 (Die Empfehlungen basieren auf einer systematischen Literaturrecherche (Suchdatum: Januar 2013).)

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)*

Referenzen:
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

In der Zweitlinientherapie nach Zytokinen können Sorafenib oder Pazopanib als Alternative zu Axitinib eingesetzt werden. *(Empfehlungsgrad 0, Level of Evidence 1+, Konsens)*

Referenzen:
321. Sternberg, C.N., et al., Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol, 2010. 28(6): p. 1061-8.
322. Escudier, B., et al., Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med, 2007. 356(2): p. 125-34. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/17215530

Nur nach Versagen von mindestens einem VEGF-Inhibitor soll Everolimus eingesetzt werden. *(Empfehlungsgrad A, Level of Evidence 1+, Konsens)*

Referenzen:
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 6: VEGF-Inhibitoren

VEGF-Inhibitoren	Anwendungsgebiete
Axitinib	Zweitlinie nach Sunitinib oder Zytokinen
Bevacizumab	Erstlinie
Pazopanib	Erstlinie oder nach Zytokinen
Sorafenib	nach Zytokinen
Sunitinib	Erstlinie

Tabelle 7: mTOR-Inhibitoren

mTOR-Inhibitoren	Zulassung
Everolimus	nach VEGF-Versagen
Temsirolimus	Erstlinie, ungünstiges Risikoprofil

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. Der Einsatz von Zytokinen in der Erstlinientherapie findet praktisch nicht mehr statt… Die Wahl in der Zweitlinie richtet sich damit nach der in der Erstlinie eingesetzten Substanz. Nach Temsirolimus in der Erstlinie ist formal keine weitere Therapie durch randomisierte kontrollierte Studien gesichert, prinzipiell wird jedoch eine Folgetherapie mit einem VEGFR-TKI empfohlen. Die Beobachtung wird durch die Daten der RECORD-3-Studie unterstützt, die den sequenziellen Einsatz von Sunitinib und Everolimus untersucht hat und Effektivität in der Zweitlinienbehandlung mit Sunitinib aufzeigen konnte. Für Temsirolimus fehlen prospektive Daten. 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). 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). <u>Referenzen:</u> 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-

<table>
<tr><td></td><td>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.</td></tr>
<tr><td rowspan="2">Dutch Dieticians Oncology Group, 2012 [4].

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

<u>Grundlage der Leitlinie</u>

– 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.
– October 2009 search 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, 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

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)

Referenzen

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 pazopanib results in an improvement in PFS compared to placebo with good or intermediate risk (according to MSKCC criteria) clear cell renal cell carcinoma patients. (Level 2: A2)

Referenzen

560 Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in Locally Advanced or Metastatic Renal Cell Carcinoma: Results of a Randomized Phase III Trial. J Clin Oncol 2010 Jan 25.

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)

Referenzen

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.

There are currently no study results regarding second-line treatment of non-clear cell RCC. Level 4: Opinion of guideline development group members

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Kang SK et al., 2016 [11]. Efficacy and Safety of Selective Vascular Endothelial Growth Factor Receptor Inhibitors Compared with Sorafenib for Metastatic Renal Cell Carcinoma: a Meta-analysis of Randomised Controlled Trials	**Fragestellung** Selective vascular endothelial growth factor receptor (VEGFR) inhibitors have the potential for greater potency and less off-target toxicity compared with multikinase tyrosine kinase inhibitors in the treatment of metastatic renal cell carcinoma. We carried out a meta-analysis to determine quantitatively the differences in comparative efficacy and tolerability between these newer, selective agents and the multikinase inhibitors. **Methodik** Population: patients with metastatic (stage IV) renal cell carcinoma Intervention und Komparator: selective VEGFR agents versus multitargeted tyrosine kinase inhibitors (sunitinib, sorafenib or pazopanib) Endpunkt: PFS, objective response rate (ORR), overall survival (OS) and Discontinuation due to Adverse Events (DAE) and quantitatively summarised the side-effect profiles of selective VEGFR agents versus multitargeted tyrosine kinase inhibitors. Suchzeitraum: No date restrictions were applied. The search was updated until 1 February 2015. Datenbanken: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews andWeb of Science. Reviewarticles were also used to identify any additional references of trials and specific selective VEGFR agents that may have been tested in trials. In addition, non-published trials were searched using the conference proceedings of the American Society of Clinical Oncology for abstracts presented at meetings. We also searched clinical trial registries for additional trials that may have been conducted. Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 trials were included in qualitative and quantitative analyses. These four trials included 2098 patients, 553 receiving axitinib, 260 treated with tivozanib and 284 treated with dovitinib. Trials involving comparison of a selective, targeted VEGFR inhibitor with a placebo were excluded. Qualitätsbewertung der Studien: methodological quality of included clinical trials were assed according to criteria established by the Cochrane Collaboration.

	Ergebnisse RoB: low • Treatment with one of the more potent VEGFR drugs was used as a first-, second-line or third-line therapy in the included trials. • When the selective VEGFR inhibitor was received as a second-line treatment, patients previously underwent a VEGF-targeted therapy (i.e. sunitinib, bevacizumab), temsirolimus or cytokine therapies. • Quantitative pooling showed a 22% reduction in the hazard of disease progression with the use of newer VEGFR inhibitors (four trials, 2098 patients, relative risk 0.78; 95% confidence interval 0.69e0.87; Figure 2). A subgroup analysis was carried out for PFS based on whether the selective VEGFR drug was used as a first-line versus a second- or third-line agent. There was a 21% reduction in the risk of disease progression with use of the newer drug as a first-line agent (two trials, 452 patients, relative risk 0.79; 95% confidence interval 0.67e0.92) and a 22% reduction in the relative risk for disease progression with use of the newer drug as a second- or third-line agent (two trials, 645 patients, relative risk 0.78; 95% confidence interval 0.59e0.98). **Fazit der Autoren** Although selective VEGFR inhibitors are associated with similar overall survival as multikinase inhibitor sorafenib, they show significant improvement in progression-free survival, regardless of first-line or later use, and ORR compared with sorafenib. Tolerability due to toxicities is similar. **Hinweis FB Med**: Pooling von first-, second- und third-line.

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])

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) **am 15.11.2016**

#	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 (Word variations have been searched)
3	cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*:ti,ab,kw (Word variations have been searched)
4	#2 and #3
5	hypernephroma* or rcc:ti,ab,kw (Word variations have been searched)
6	#1 or #4 or #5
7	#1 or #4 or #5 Publication Year from 2016 to 2016, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 15.11.2016

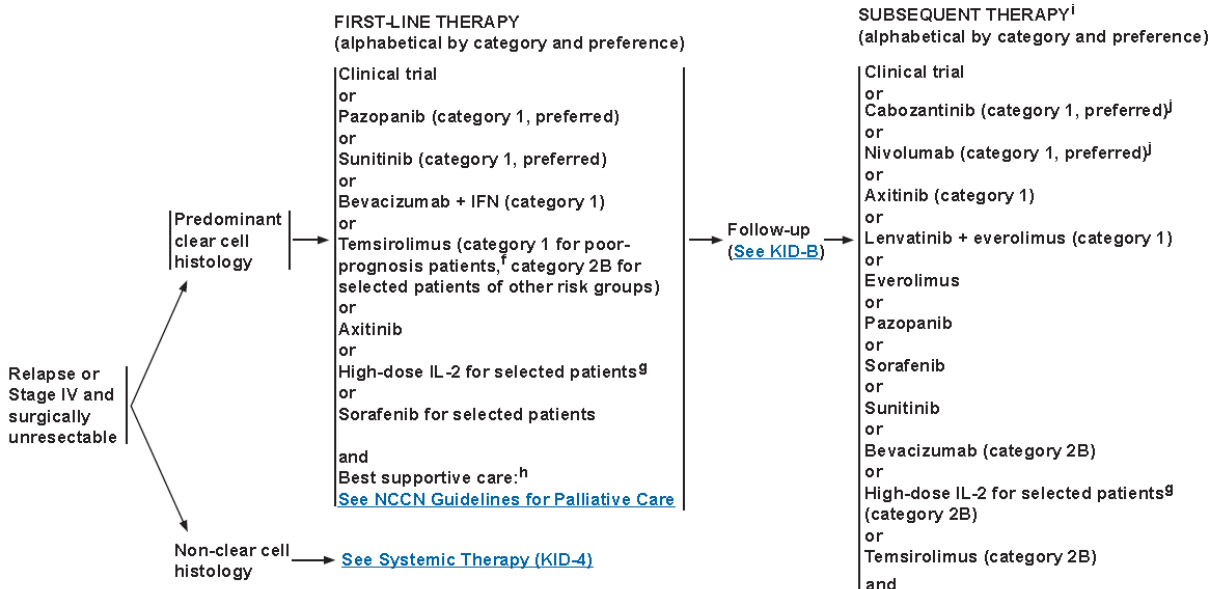
#	Suchfrage
1	carcinoma, renal cell[MeSH Terms]
2	(((((((renal[Title/Abstract]) AND cell[Title/Abstract])) OR kidney*[Title/Abstract]) OR nephroid*[Title/Abstract]) OR hypernephroid*[Title/Abstract]) OR grawitz*[Title/Abstract]) OR collecting duct[Title/Abstract]
3	((((((cancer*[Title/Abstract]) OR tumor*[Title/Abstract]) 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 ("2016/03/31"[PDAT] : "2016/11/15"[PDAT])
16	(#15) NOT "The Cochrane database of systematic reviews"[Journal]

Leitlinien in Medline (PubMed) am 15.11.2016

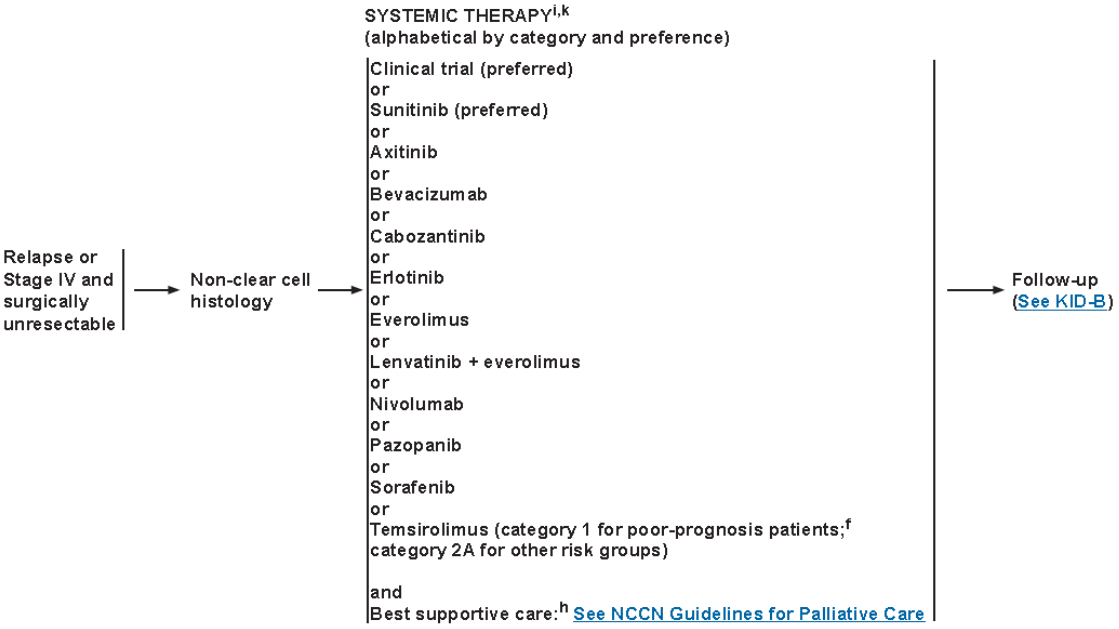
#	Suchfrage
1	carcinoma, renal cell[MeSH Terms]
2	"Kidney Neoplasms"[Mesh:NoExp]
3	(((((((renal[Title/Abstract]) AND cell[Title/Abstract])) OR kidney*[Title/Abstract]) OR nephroid*[Title/Abstract]) OR hypernephroid*[Title/Abstract]) OR grawitz*[Title/Abstract]) OR collecting duct[Title/Abstract]
4	((((((cancer*[Title/Abstract]) 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 ("2016/03/31"[PDAT] : "2016/11/15"[PDAT])

Anhang



[f]Poor-prognosis patients, defined as those with ≥3 predictors of short survival. See Predictors of Short Survival Used to Select Patients for Temsirolimus (KID-C).
[g]Patients with excellent performance status and normal organ function.
[h]Best supportive care can include palliative RT, metastasectomy, bisphosphonates, or RANK ligand inhibitors for bony metastases.
[i]In clear cell and non-clear cell RCC with predominant sarcomatoid features, gemcitabine + doxorubicin (category 2B) and gemcitabine + sunitinib (category 2B) have shown benefit.
[j]Based on the results of phase III trials, eligible patients should preferentially receive this agent over everolimus. See Discussion.

Abbildung 1: NCCN Guidelines. Kidney Cancer Version 2.2017 – Treatment (1)



[f]Poor-prognosis patients, defined as those with ≥3 predictors of short survival. See Predictors of Short Survival Used to Select Patients for Temsirolimus (KID-C).
[h]Best supportive care can include palliative RT, metastasectomy, bisphosphonates, or RANK ligand inhibitors for bony metastases.
[i]In clear cell and non-clear cell RCC with predominant sarcomatoid features, gemcitabine + doxorubicin (category 2B) and gemcitabine + sunitinib (category 2B) have shown benefit.
[k]Partial responses have been observed for cytotoxic chemotherapy (carboplatin + gemcitabine, carboplatin + paclitaxel, or cisplatin + gemcitabine) with collecting duct or medullary subtypes.

Abbildung 2: NCCN Guidelines. Kidney Cancer Version 2.2017 – Treatment (2)

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

RCC type	MSKCC risk group [319]	First-line	LE^	Second-Line after VEGF therapy*	LE^	Third-line*	LE^	Later lines	LE
Clear cell*	Favourable, intermediate and poor	sunitinib pazopanib bevacizumab + IFN-α (favourable-intermediate only)	1b 1b 1b	based on OS: nivolumab based on PFS: cabozantinib axitinib sorafenib# everolimus&	2a 2a 2a 2a 2a	after VEGF therapy: nivolumab cabozantinib everolimus& after VEGF and mTOR therapy: sorafenib after VEGF and nivolumab: cabozantinib axitinib everolimus	2a 2a 2a 1b 4 4 4	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; 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 [319] risk plus metastases in multiple organs. Evidence for subsequent therapies unclear, making this option less appealing.

 # 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.
& everolimus was inferior in terms of OS to nivolumab and in terms of PFS to cabozantinib and should not routinely be given where other superior agents are available.

Abbildung 3: EAU Guidelines on Renal Cell Carcinoma (Ljundberg B et al. 2016)

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