Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2017-B-235 Cabozantinib

Stand: November 2017

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Cabozantinib
[zur Behandlung von nicht-vorbehandelten Erwachsenen mit fortgeschrittenem Nierenzellkarzinom]

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.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• Negativer Beschluss über eine Änderung der AM-RL: Anlage VI – Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten - Inhalatives Interleukin-2 (Proleukin®) zur Therapie des Nierenzellkarzinoms – 8. Juni 2016 • Beschluss des G-BA über Rücknahme eines Auftrags an die Expertengruppe Off-Label Im Fachbereich Onkologie: Interferon-alpha und Interleukin-2-basierte Immunochemotherapien beim metastasierten Nierenzellkarzinom und in der adjuvanten Therapie – 15. Oktober 2009
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 bewertendes Arzneimittel:	
Cabozantinib L01XE26 Cabometyx®	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung/Zulassungsantrag:</u> Cabometyx ist indiziert für die Behandlung des fortgeschrittenen Nierenzellkarzinoms (RCC) bei nicht-vorbehandelten Erwachsenen mit intermediärem oder ungünstigem Risikoprofil nach IMDC Kriterien.
Monoklonale Antikörper	
Bevacizumab L01XC07 Avastin®	Bevacizumab wird in Kombination mit Interferon alfa-2a zur First-Line-Behandlung von erwachsenen Patienten mit fortgeschrittenem und/oder metastasiertem Nierenzellkarzinom angewendet
Tyrosin-Kinase-Inhibitoren	
Sunitinib L01XE04 Sutent®	<u>Metastasierte Nierenzellkarzinome (mRCC)</u> SUTENT wird bei Erwachsenen zur Behandlung fortgeschrittener/metastasierter Nierenzellkarzinome (mRCC) eingesetzt.
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
Tivozanib L01XE34 Fotvida®	Fotivda dient als Erstlinientherapie bei erwachsenen Patienten mit fortgeschrittenem Nierenzellkarzinom (NZK) sowie als Therapie bei erwachsenen Patienten, die noch nicht mit VEGFR- und mTOR-Signalweginhibitoren behandelt wurden und bei denen es nach einer vorherigen Cytokin-Therapie für fortgeschrittene NZK zur Krankheitsprogression kam.
mTOR-Inhibitoren	
Temsirolimus L01XE09 Torisel®	<u>Nierenzellkarzinom</u> Torisel ist angezeigt zur first-line-Behandlung des fortgeschrittenen Nierenzellkarzinoms (renal cell carcinoma, RCC) bei erwachsenen Patienten, die mindestens 3 von 6 prognostischen Risikofaktoren aufweisen (siehe Abschnitt 5.1).

II. Zugelassene Arzneimittel im Anwendungsgebiet

Zytokine	
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.
Interferon alfa-2a L03AB04 Roferon®-A	Roferon-A wird für die Behandlung der folgenden Erkrankungen angewendet: • Fortgeschritenes Nierenzell-Karzinom

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer
Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V
Vorgang: 2017-B-235 (Cabozantinib)

Auftrag von:	Abt. AM
bearbeitet von:	Abt. FB Med
Datum:	11.10.2017

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

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation Nierenzellkarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 09.08.2017 abgeschlossen. Die Suche erfolgte in den aufgeführten 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, CCO, ESMO, NCCN, NCI. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.
Die Recherche ergab 1123 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 15 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

zur Behandlung des fortgeschrittenen Nierenzellkarzinoms (RCC) bei nicht-vorbehandelten Erwachsenen mit intermediärem oder ungünstigem Risikoprofil nach IMDC Kriterien.

Hinweis:
Cochrane Reviews sowie systematische Reviews sind im Folgenden untergliedert in die zwei Indikationen. Indikation 1 wird hierbei mit „Erstlinie“ und Indikation 2 mit „Zweitlinie nach Zytokin-Therapie“ bezeichnet.
Bei den Leitlinien wurden die Empfehlungen zu den zwei Indikationen mittels der Bezeichnungen „Erstlinie“ bzw. „Zweitlinie nach Zytokin-Therapie“ innerhalb einer Extraktion hervorgehoben.

Abkürzungen:

AA	Antiangiogenic agents
AE	adverse events
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CC	Clear cell
CCO	Cancer Care Ontario
CR	Complete response
DAHTA	Deutsche Agentur für Health Technology Assessment
DAE	discontinuation of therapy due to adverse events
DoR	Duration of response
DRKS	Deutsches Register Klinischer Studien
EAU	European Association of Urology
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
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IRC	Independent review committee
ISRCTN	International Standard Randomised Controlled Trial Number
LoE	Level of evidence
mRCC	metastatic renal cell carcinoma
MSKCC	Memorial Sloan-Kettering Cancer Center Score
mTOR	Mammalian target of rapamycin inhibitors
NCCN	National Comprehensive Cancer Network
NCI	U.S. 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
PEBC	Program in Evidence-Based Care
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
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 [3]. 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 – Axitinib, vom 21. März 2013 siehe auch: IQWiG, 2012 [7]. Axitinib – Nutzenbewertung gemäß § 35a SGB V (IQWiG-Berichte – Nr. 149)	<u>Zugelassenes Anwendungsgebiet von Axitinib (Inlyta®)</u> gemäß Fachinformation (Stand: September 2012): Inlyta® ist angezeigt zur Behandlung des fortgeschrittenen Nierenzellkarzinoms bei erwachsenen Patienten nach Versagen von vorangegangener Therapie mit Sunitinib oder einem Zytokin. **Nach vorangegangener Therapie mit einem Zytokin** <u>Zweckmäßige Vergleichstherapie</u>: Sorafenib <u>Ausmaß und Wahrscheinlichkeit des Zusatznutzens:</u> Hinweis für einen geringen Zusatznutzen.
IQWiG, 2017 [8]. Axitinib (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V Ablauf Befristung IQWiG-Berichte – Nr. 519	<u>Fragestellung</u> Nutzenbewertung des Wirkstoffs Axitinib gemäß § 35a SGB V <u>Population</u> Erwachsene Patienten mit fortgeschrittenem Nierenzellkarzinom nach Versagen von vorangegangener Therapie mit einem Zytokin <u>Ergebnis</u> **Nach vorangegangener Therapie mit einem Zytokin** <u>Zweckmäßige Vergleichstherapie:</u> Sorafenib <u>Ausmaß und Wahrscheinlichkeit des Zusatznutzens:</u> Anhaltspunkt für einen beträchtlichen Zusatznutzen *<u>Hinweis</u>:* *G-BA: Nutzenbewertungsverfahren zum Wirkstoff Axitinib (Neubewertung nach Fristablauf)* ***Verfahrensstatus:** Beschlussfassung wird vorbereitet*

Cochrane Reviews zur Erstlinie

Unverzagt S et al., 2017 [14]. Immunotherapy formetastatic renal cell carcinoma (Review)	**1. Fragestellung** To assess the effects of immunotherapies either alone or in combination with standard targeted therapies for the treatment of metastatic renal cell carcinoma and their efficacy to maximize patient benefit.
	2. Methodik ***Population*** - Participants diagnosed with all types of histologically confirmed mRCC including stage IV (T4 any N M0, any T any N M1) - We excluded studies that focused on locally advanced disease. ***Intervention*** at least one immunotherapeutic agent: 1. ILs alone or combined with other immunotherapy or targeted therapies. 2. IFN- α alone or combined with other immunotherapy or targeted therapies. 3. Vaccine treatment (dentritic cell (DC)-mediated, Bacillus Calmette-Guérin (BCG) with tumour antigen, tumourassociated peptides) alone or in combination with other immunotherapy or targeted therapies. 4. Adoptive T-cell therapies. 5. Targeted immunotherapy (checkpoint inhibitors) either alone or in combination with other immunotherapy or targeted therapies. 6. Other immunotherapies identified from the searches. ***Komparator*** current standard therapy in the form of: - targeted therapies in first-, second- or third-line therapies; - immunotherapies and targeted therapies (IFN-α plus bevacizumab) in first-line therapy Comparisons 1. IFN-α alone versus standard targeted therapy in first-line therapy of mRCC. 2. IFN-α combined with targeted therapies versus standard targeted therapy in first-line therapy of mRCC. 3. IFN-α alone versus IFN-α plus bevacizumab in first-line therapy of mRCC. 4. IFN- α plus bevacizumab versus standard targeted therapies in first-line therapy of mRCC.* 5. Vaccine treatment versus standard therapies in first-line therapy

	of mRCC. 6. Targeted immunotherapies versus standard targeted therapy in previously treated patients with mRCC.* *We identified no studies comparing current standard therapies against adoptive T-cell therapies (experimental intervention 4) and other immunotherapies (experimental intervention 6). ***Endpunkte*** Primary outcomes 1. Overall survival (OS) including one-year mortality. 2. Quality of life (QoL). 3. Adverse events (AEs) (grade 3 or greater). Secondary outcomes 1. Progression-free survival (PFS) (progression may have been measured using clinical or radiological indices). 2. Tumour remission (both partial and complete remission). ***Suchzeitraum (Aktualität der Recherche):*** bis Oktober 2016 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 8 RCTs/quasi-RCTs, 4732 participants ***Qualitätsbewertung der Studien:*** - Cochrane's 'Risk of bias' assessment tool - quality of evidence using GRADE
	3. Ergebnisdarstellung Qualität der Studien  **Erstlinie** <u>First-line therapy (in previously untreated patients)</u>

	IFN-α compared with temsirolimus or sunitinib - probably increases one-year overall mortality (RR 1.30, 95% CI 1.13 to 1.51; 2 studies; 1166 participants; moderate-quality evidence) - may lead to similar quality of life (QoL) (no clinically important differences e.g. MD -5.58 points, 95% CI -7.25 to -3.91 for Functional Assessment of Cancer - General (FACT-G); 1 study; 730 participants; low-quality evidence) - may slightly increase the incidence of adverse events (AEs) grade 3 or greater (RR 1.17, 95% CI 1.03 to 1.32; 1 study; 408 participants; low-quality evidence). **IFN-α + temsirolimus compared with temsirolimus** - probably no difference for one-year overall mortality (RR 1.13, 95% CI 0.95 to 1.34; 1 study; 419 participants; moderate-quality evidence) - may increase the incidence of AEs of 3 or greater (RR 1.30, 95% CI 1.17 to 1.45; 1 study; 416 participants; low-quality evidence) **IFN-α compared with IFN-α + bevacizumab** - may slightly increase one-year overall mortality (RR 1.17, 95% CI 1.00 to 1.36; 2 studies; 1381 participants; low-quality evidence) - may decrease the incidence of AEs of grade 3 or greater (RR 0.77, 95% CI 0.71 to 0.84; 2 studies; 1350 participants; moderate-quality evidence) **IFN-α + bevacizumab compared with sunitinib** - may lead to similar one-year overall mortality (RR 0.37, 95% CI 0.13 to 1.08; 1 study; 83 participants; low-quality evidence) - may lead to similar incidence of AEs of grade 3 or greater (RR 1.18, 95% CI 0.85 to 1.62; 1 study; 82 participants; low-quality evidence) **Zweitlinie nach Zytokin-Therapie** keine Studie eingeschlossen
	4. Fazit der Autoren Evidence of moderate quality demonstrates that IFN-α monotherapy increases mortality compared to standard targeted therapies alone, whereas there is no difference if IFN is combined with standard targeted therapies. Evidence of low quality demonstrates that QoL is worse with IFN alone and that severe AEs are increased with IFN alone or in combination. There is low-quality evidence that IFN-α alone increases mortality but moderate-quality evidence on decreased AEs compared to IFN-α plus bevacizumab. Low-quality evidence

	shows no difference for IFN-α plus bevacizumab compared to sunitinib with respect to mortality and severe AEs.

Cochrane Reviews zur Zweitlinie nach Zytokin-Therapie

- keine vorhanden -

Systematische Reviews

Systematische Reviews zur Erstlinie

Rousseau B et al., 2016 [13] First-line antiangiogenics for metastatic renal cell carcinoma: A systematic review and network meta-analysis	**1. Fragestellung** performing a systematic review and network meta-analysis in order to compare clinical outcomes and safety profiles of five recommended first-line antiangiogenic drugs in cytokine-naive patients with mRCC
	2. Methodik ***Population*** mRCC inpatients not pretreated with cytokines ***Intervention/Komparator*** first-line treatment: any pair of the following interventions: placebo, interferon alpha-2a, sorafenib, pazopanib, sunitinib, axitinib, bevacizumab plus interferon alpha-2a ***Endpunkte*** - objective response rate (ORR, including complete and partial response) - disease control rate (DCR, including ORR and stable disease) according to RECISTvs.1.0 or 1.1 - PFS, OS - safety outcomes of interest: number of patients experiencing drug temporary interruption, permanent discontinuation, dose reduction, overall rate of all and high-grade (grade ≥3) toxicities, hypertension, fatigue, nausea, anorexia, loss of weight, hand-foot skin reaction (HFSR), diarrhea, and anemia. ***Suchzeitraum(Aktualität der Recherche)*** bis Juli 2014 ***Netzwerk-Metaanalyse*** Bayesian hierarchical model. This model incorporates heterogeneity between multiple trials of the same pairof treatments and adds a random effect for each treatment pair to allow for inconsistency in the model. ***Anzahl eingeschlossene Studien/Patienten (Gesamt)*** 9 RCTs / 4282 patients (19 treatment arms in network meta-analysis)

Qualitätsbewertung der Studien:
Risk of bias according to the Cochrane Handbook

3. Ergebnisdarstellung

Studiencharakteristika und -qualität

Characteristics of included studies and efficacy results.

Study, year	RCT treatment arms	No. of patients	Cross-over, n	Median PFS			Median OS		
				mo	HR (CI 95%)	p value	mo	HR (CI 95%)	p value
Escudier et al. (2007a, 2009a), Negrier et al. (2010)[a]	Sorafenib	7784	NR	5.8	0.48 (0.32–0.73)	NR	17.8[b]	0.88	0.146[b]
	Placebo			2.8			15.2[b]	(0.74–1.04)[b]	
Motzer et al. (2007, 2009)	Sunitinib	375	0	11	0.539	<0.001	26.4	0.821	0.051
	Interferon alpha-2a	375	25	5	(0.451–0.643)		21.8	(0.673–1.001)	
Motzer et al. (2013b, 2014)	Pazopanib	557	NA	8.4	1.05 (0.90–1.22)	NR	28.4	0.91	0.28
	Sunitinib	553		9.5			29.3	(0.76–1.08)	
Rini et al. (2008, 2010)	Bevacizumab + Interferon alpha-2a	363	NA	8.5	0.71 (0.61–0.83)	< 0.0001	18.3	0.86	0.069
	Interferon alpha-2a	369		5.2			17.4	(0.73–1.01)	
Escudier et al. (2007b), Melichar et al. (2008), Escudier et al. (2010)	Bevacizumab + Interferon alpha-2a	327	0	10.2	0.61 (0.51–0.73)	<0.0001	23.3	0.86	0.1291
	Placebo+ Interferon alpha-2a	322	13	5.4			21.3	(0.72–1.04)	
Sternberg et al. (2010, 2013)[a]	Pazopanib	155	NR	11.1	0.4 (0.27–0.60)	<0.0001	22.9	0.82	NR
	Placebo	78		2.8			23.5	(0.57–1.16)	
Escudier et al. (2009b)	Sorafenib	97	44	5.7	0.88 (0.61–1.27)	0.5	NR	NR	NR
	Interferon alpha-2a	92	50	5.6					
Négrier et al. (2011)	Temsirolimus ± Bevacizumab	88	NA	8.2	NR	NR	NR	NR	NR
	Sunitinib	42		8.2					
	Bevacizumab ± Interferon alpha-2a	40		16.8					
Hutson et al. (2013)	Axitinib	192	NA	10.1	0.77 (0.56–1.05)	0.036 (unilateral)	NR	NR	NR
	Sorafenib	96		6.5					

PFS = progression-free survival; OS = overall survival; HR = hazard ratio; CI 95% = confidence interval 95%; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; reported; NA = not applicable.
[a] Data restricted to cytokine-naïve patients.
[b] Data including cytokine-naive and cytokine-pretreated patients.

Hinweis: „No. of patients" in der ersten Zeile heißt 77 und 84 anstatt 7784.

Risk of bias assessment

Study	Year	Sequence generation	Allocation concealment	Blinding	Incomplete outcome	Selective outcome report	Other source of bias	Comments
Escudier et al. [5]	2007	low	low	low	low	low	no	-
Motzer et al.[4]	2007	low	low	high	low	low	no	Not blinded
Motzer et al. [16]	2013	low	low	high	low	low	no	Not blinded
Rini et al. [8]	2008	low	low	high	unclear	low	no	CONSORT diagram incomplete
Escudier et al.[9]	2007	low	low	low	unclear	low	no	Toxicity not evaluated at primary endpoint cut off
Sternberg et al. [29]	2010	low	low	low	low	low	yes	Performed mainly in countries without access to other antiangiogenics during trial
Escudier et al. [31]	2009	low	low	high	low	low	no	-
Negrier et al. [43]	2011	low	low	high	unclear	low	yes	Imbalance in patient characteristics after randomization
Hutson et al [10]	2013	low	low	high	low	low	no	Not blinded ; different number of drug definitive interruption in the text and the flow chart

Wirksamkeit

Direkte Vergleiche (Meta-Analyse):
Antiangiogenic agents vs placebo or interferon alpha-2a

<u>Progression-free survival</u>
Antiangiogenic agents significantly improved PFS compared with placebo or interferon alpha-2a (HR = 0.60; 95% CI 0.51–0.62; p < 0.00001), signifkante Heterogenität (p=0.01, I^2= 66%) (6 studies).

<u>Overall survival</u>
Antiangiogenic drugs significantly prolonged OS compared with placebo or interferon alpha-2a (HR = 0.85; 95% CI 0.78–0.93, p = 0.0004), keine signifkante Heterogenität (p=0.99, I^2= 0%) (5 studies).

Objective response rate

Antiangiogenic drugs significantly improved ORR compared with placebo or interferon alph-2a (OR = 3.96; 95% CI 1.78–8.83; p = 0.0007), signifkante Heterogenität (p=0.0002, I^2= 82%) (5 studies).

Disease control rate

Antiangiogenic drugs significantly improved DCR compared with placebo or interferon alph-2a (OR = 2.77; 95% CI 1.94–3.97; p <0.0001), keine signifkante Heterogenität (p=0.10, I^2= 52%) (4 studies).

Safety

- permanent treatment discontinuation due to toxicity: No increased risk with antiangiogenic drugs when compared with placebo or interferon alpha-2a (OR = 1.22; 95% CI 0.81–1.84; p = 0.34, I^2= 79%) (9 studies)
- temporary treatment interruption: antiangiogenic drugs were associated with a significant increase when compared with placebo or interferon alpha-2a (OR = 2.46; 95% CI1.38–4.38; p < 0.00001; I^2= 89%) (6 studies)
- dose reduction: antiangiogenic drugs were associated with a significant dose reduction when compared with placebo or interferon alpha-2a (OR = 2.13; 95% CI 1.47–3.08; p = 0.002; I^2= 77%) (7 studies)

Indirekte Vergleiche (Netzwerk-Metaanalyse)

Hinweis: Ergebnisse der Netzwerk-Metaanalyse zu den einzelnen Sicherheits-Endpunkten werden in der Synopse nicht dargestellt.

Network: 18 arms with 7 different treatmans

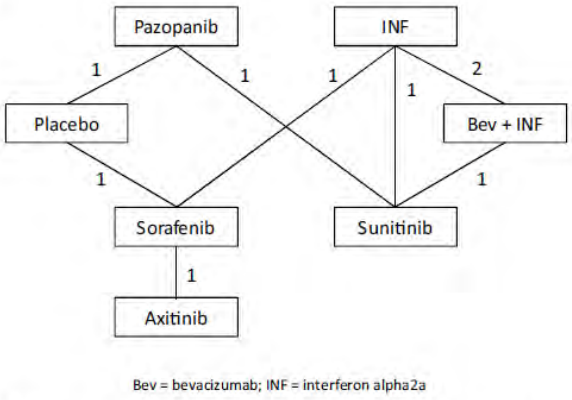


Fig. 3. Network of treatment comparisons established for the nine selected two-arm clinical trials. Lines between agents represent direct comparisons. The numbers represent the number of trial arms providing direct comparison between the angiogenic agents. Bev = bevacizumab; INF = interferon alpha2a.

6-month progression-free survival

- There was a significant increase in 6-month PFS in favor of sunitinib versus sorafenib: OR (95% CI 1.8 (1,1–3,1))
- The five antiangiogenic drugs showed statistically significant improved 6-month PFS compared with interferon alpha-2a or placebo (OR siehe Table 2).
- Treatment comparisons showed no significant difference between sunitinib, pazopanib, axitinib and beva-cizumab plus interferon alpha-2a (OR siehe Table 2).

<u>1-year survival</u>

- Treatment comparisons demonstrated a significant improvement in patients treated with pazopanib compared to those receiving interferon alpha-2a or placebo: OR (95% CI): 1,6 (1,1–2,4) bzw. 1,8 (1,2–2,7)
- A similar trend was observed for sunitinib and bevacizumab plus interferon alpha-2a compared with interferon alpha-2a: OR (95% CI): 1,4 (1,0–1,9) bzw.1,3 (1,0–1,6)
- There was no significant difference in 1-year survival between the four antiangiogenic treatment (keine Daten für Axitinib, OR siehe Table 2).

<u>Objective response rate and disease control rate</u>
OR siehe Table 2

- No significant difference in DCR between the five antiangiogenic drugs.
- All antiangiogenicdrugs showed significant improvement of DCR compared with placebo or interferon alpha2a.

Table 2
Efficacy of antiangiogenic agents in terms of 6-month progression-free survival (a), 1-year overall survival (b), and disease control rate (d) in cytokine-naive patients.

(a)						
SUN						
1,1 (0,8–1,4)	**PAZ**					
1,3 (0,9–1,9)	1,2 (0,8–1,8)	**BEV**				
1,2 (0.6–2,6)	1,1 (0.5–2,4)	1,0 (0,4–2,0)	**AXI**			
1.8 (1,1–3,1)	1.7 (0.9–2.9)	1,4 (0.8–2,4)	1,5 (0,8–2,5)	**SOR**		
2.5 (1.9–3.4)	**2.3 (1.6–3.3)**	**1.9 (1,6–2.4)**	**2,0 (1,0–4.1)**	1,4 (0.8–2,2)	**IFN**	
4.5 (2.6–7.4)	**4.1 (2.5–6.6)**	**3.4 (1.9–6.1)**	**3.6 (1.7–7.3)**	**2.4 (1.4–4.0)**	1.8 (1.0–3.1)	**PBO**
(b)						
PAZ						
1,2 (0,9–1,6)	**SUN**					
1,3 (0,8–2)	1,1 (0,7–1,5)	**BEV**				
1,6 (1,1–2,4)	1,4 (1,0–1,9)	1,3 (1,0–1,6)	**IFN**			
1,4 (0.8–2,3)	1,2 (0,6–2,0)	1,1 (0,6–1,9)	0,9 (0,4–1,5)	**SOR**		
1,8 (1,2–2,7)	1,5 (0,9–2,4)	1,4 (0,8–2,3)	1,1 (0,6–1,8)	1,3 (0,9–1,8)	**PLA**	
(c)						
PAZ						
1,0 (0,8–1,3)	**SUN**					
1,2 (0,4–3,3)	1,2 (0,4–3,1)	**AXI**				
1,6 (0,7–3,4)	1,5 (0,7–3,2)	1,3 (0,6–2,4)	**SOR**			
1.6 (0,9–2,7)	1.5 (0,9–2,4)	1.3 (0,5–3,5)	1.0 (0,4–2,2)	**BEV**		
3.4 (2.2–5.3)	**3.3 (2.3–4.6)**	**2.8 (1.1–7.0)**	**2,2 (1.1–4.3)**	**2.1 (1.5–3.0)**	**IFN**	
7.6 (2.6–24)	**7.3 (2.5–22)**	**6.3 (2.3–18)**	**4.8 (2.3–11)**	**4.8 (1.6–15)**	2.2 (0.8–6.4)	**PLA**

Results are the odd ratio (OR) with 95% confidence interval in parentheses. Statistically significant results are in bold. The ORs > 1 favor the column-defining treatment. The ORs < 1 favor the line-defining treatment. SUN = sunitinib; PAZ = pazopanib; BEV = bevacizumab; IFN = interferon alpha-2a; SOR = sorafenib; PLA = placebo.

<u>Safety</u>

- <u>permanent treatment discontinuations</u>: Sunitinib showed significantly less adverse event-related permanent treatment

discontinuations compared with bevacizumab plus interferon alpha-2a (OR = 3.2; 95% CI 1.1–11; Supplementary Table 5 and Supplementary Fig. 3). Treatment comparisons showed no other significant difference between placebo, sunitinib, pazopanib, axitinib and bevacizumab plus interferon alpha-2a (OR siehe Tabelle).

PLA						
1,0 (0,2-4,5)	**SUN**					
1,2 (0,3-4.0)	1,2 (0,3-3.9)	**PAZ**				
1,2 (0,3-4.2)	1,2 (0,2-5.6)	1,0 (0,2-4,8)	**SOR**			
1,5 (0,3-7.7)	1,6 (0,5-4.9)	1,3 (0,3-6,2)	1,3 (0,3-5,3)	**IFN**		
3,1 (0.6-19)	**3,2 (1.1-11)**	2,7 (0,6-15)	2,6 (0,5-14)	2,0 (0,8-5,2)	**BEV**	
1.7 (0.2-19)	1.8 (0.1-22)	1.5 (0.1-19)	1.5 (0.2-11)	1.1 (0.1-12)	0.6 (0.0-6.7)	**AXI**

- Temporary treatment interruption was not tested because of network inconsistency.

4. Fazit der Autoren

Our review and direct meta-analysis showed that most currently recommended first-line antiangiogenics provide significant 6-month PFS and 1-year OS survival benefit over interferon alpha-2a and placebo in mRCC. Bevacizumab plus interferon alpha-2a seemed to be associated with a higher rate of adverse event-related permanent discontinuations. Axitinib, pazopanib and sunitinib shared comparable efficacy but presented heterogeneous safety profiles for patients with mRCC. These diverse efficacy-toxicity patterns may help clinicians in personalizing first-line antiangiogenic treatment.

5. Hinweise durch FB Med

- Das Fazit bezüglich der Vergleiche zwischen den einzelnen antiangiogenetischen Susbstanzen beruht auf den indirekten Vergleichen der Netzwerk-Metaaanalyse.
- 1 RCT (mit Vergleich Sorafenib vs. Plazebo) beinhaltet auch Zytokin-vorbehandelte Patienten. Bei diesem ist unklar, ob die Gruppe der vorbehandelten Patienten aus den Vergleichen zur Wirksamkeit in Zytokin-naiven Patienten ausgeschlossen wurden.
- Bezüglich der direkten Vergleiche: 2 RCTs verglichen die Wirksmakeit von antiangiongenetischen Therapien ausschließlich gegen Plazebo.
- Teils stimmen die p-Werte im Text nicht mit denen in den Grafiken überein. Extrahiert wurden die p-Werte aus den Grafiken. Die Interpreation der Ergebnisse ändert sich nicht durch die unterschiedlichen p-Werte.

Wang L et al., 2015 [15].

Therapeutic effects and

1. Fragestellung

To compare the therapeutic effects and adverse events (AE) of current first-line treatments of advanced RCC, including sorafenib, sunitinib, temsirolimus, and the combination of bevacizumab and IFN-α.

2. Methodik

associated adverse events of first-line treatments of advanced renal cell carcinoma (RCC): a meta-analysis	***Population*** advanced RCC without previously cancer immunotherapy or other molecular targeted therapy ***Intervention*** antiangiogenic agents individually or in combination with interferon, without surgery or other non-antiangiogenic treatment ***Komparator*** IFN ***Endpunkte*** - tumor progression, - overall response rate (ORR), - disease control rate (DCR) - median progression-free survival (PFS) - median overall survival (OS) - number of patients who suffered grade 3/4 adverse events, ***Suchzeitraum (Aktualität der Recherche)*** bis Oktober 2014 ***Anzahl eingeschlossene Studien/Patienten (Gesamt)*** 5 RCTs / 2736 Patienten ***Qualitätsbewertung der Studien:*** - Cochrane Risk of Bias Tool - LoE classification: A= appropriate and sufficient support of index of outcome assessment that with minimal risk of bias; B= one or more high or unclear risk of bias among the quality components and with middle-level risk of bias; C= three or more high or unclear risk of bias among the quality components and with the highest level of bias
	3. Ergebnisdarstellung ***Studiencharakteristika und -qualität:*** moderate quality of the included trials **Table 1** Summary of trails involved *R* randomized, *S* stratification, *RPB* random permuted blocks, *BR* blind reviewer, *DB* double blind, *NB* non-blind, *F* follow-up, *C* controlled, *ITT* intent-to-treat ***Wirksamkeit gegenüber INF*** <u>Tumor progression</u> - signifkanter Vorteil von sorafenib (1 RCT; n=189), sunitinib (1 RCT,

References	Quality components	Quality level	*N*	Intervention	Control
Hudes et al. [10]	R; S and RPB; C; BR; F; ITT	B	416	Temsirolimus, temsirolimus + IFN-α-2a	IFN-α-2a
Escudier et al. [16]	R; S and RPB; C; DB; F; ITT	A	649	Bevacizumab + IFN-α (IFN)	IFN-α and placebo
Rini et al. [17]	R; S and RPB; C; NB; F; ITT	B	732	Bevacizumab + IFN-α (IFN)	IFN-α
Motzer et al. [18]	R; S and RPB; C; BR; F; ITT	B	750	Sunitinib	IFN-α-2a (IFN)
Escudier et al. [19]	R; S; C; BR; F; ITT	B	189	Sorafenib	IFN-α-2a (IFN)

	n=750), temsirolimus (1 RCT n=416) vs INF: Pooled effect estimate (3 RCT): OR 0.35 [95% CI 0.26;0.48], p<0.001; keine signifikante Heterogenität: p=0.91, I^2=0% Kein signifikanter Unterschied zwischen den Subgruppen: multikinase inhibitors and temsirolimus (p=0.66) - signifkanter Vorteil von Bevacizumab+INF vs INF (2 RCT; n=1327): OR 0.64 [95%CI 0.42;0.99]; p<0.001; keine signifikante Heterogenität: p=0.07, I^2 =69% <u>Objective response rate (ORR)</u> - kein signifkanter Unterschied: sorafenib (1 RCT; n=189), sunitinib (1 RCT, n=750), temsirolimus (1 RCT n=416) vs INF: Pooled effect estimate OR 2.06 [95 % CI 0.53;7.95], p=030; signifikante Heterogenität: p<0.001, I^2=90% Kein signifikanter Unterschied zwischen den Subgruppen: multikinase inhibitors and temsirolimus (p=0.94) - signifkanter Vorteil von Bevacizumab+INF vs INF (2 RCT; n=1327): OR 2.56 [95% CI 1.91–3.42]; p<0.001; keine signifikante Heterogenität: p=0.20, I^2 =40% <u>Disease control rate (DCR)</u> - signifkanter Vorteil von sorafenib (1 RCT; n=189), sunitinib (1 RCT, n=750), temsirolimus (1 RCT, n=416) vs INF: Pooled effect estimate OR 2.90 [95%CI 2.23; 3.78]; p<0.001; keine signifikante Heterogenität: p=0.41, I^2=0% Kein signifikanter Unterschied zwischen den Subgruppen: multikinase inhibitors and temsirolimus (p=0.56) - signifkanter Vorteil von Bevacizumab+INF vs INF (2 RCT; n=1327): OR 2.14 [95%CI 1.65; 2.78]; p<0.001; keine signifikante Heterogenität: p=0.74, I^2 =0% <u>Median progression-free survival</u> - kein signifikanter Unterschied: sorafenib (1 RCT; n=189), sunitinib (1 RCT, n=750) vs INF: Pooled effect estimate HR 0.67 [95%CI 0.42;1.08], p=0.10; I^2=82% - signifkanter Vorteil von Bevacizumab+INF vs INF (2 RCT; n=1350): HR 0.68 [95%CI 0.60; 0.76], p<0.001; I^2 =0% <u>Median overall survival</u> - kein signifikanter Unterschied: sunitinib (1 RCT, n=735) vs INF: HR 0.82 [95%CI 0.67; 1.00]; p=0.05; I^2=0% - signifkanter Vorteil von Bevacizumab+INF vs INF (2 RCT; n=1350): HR 0.86 [95%CI 0.76; 0.97], p=0.01; I^2 =0%

	Grade 3 or 4 adverse events - kein signifikanter Unterschied: sorafenib (1 RCT; n=189), sunitinib (1 RCT, n=750), temsirolimus (1 RCT n=416) vs INF: Pooled effect estimate OR 1.21 [95%CI 0.96;1.51], p=0.10; keine signifikante Heterogenität: p=0.60, I^2=0% Kein signifikanter Unterschied zwischen den Subgruppen: multikinase inhibitors and temsirolimus (p=0.31) - signifkanter Vorteil von Bevacizumab+INF vs INF (2 RCT; n=1350): OR 2.09 [95%CI 1.66; 2.63], p<0.001; keine signifikante Heterogenität: p=0.26, I^2 =23%
	3. Fazit der Autoren Sorafenib, sunitinib, temsirolimus, and the combination of bevacizumab with IFN are more effective in stabilizing disease [than INF]. Combined use of bevacizumab and IFN is better than sorafenib, sunitinib, and temsirolimus in ORR, PFS, and OS, but associated with higher level of AE. **4. Hinweise durch FB Med** Aussage/Fazit zum Vergleich von Bevacizumab+IFN vs Sorafenib, Sunitinib oder Temsirolimus beruht aus indirekten Vergleichen der Effektschätzer (siehe forest plots).
Iacovelli R et al., 2015 [6]. Inhibition of the VEGF/VEGFR pathway improves survival in advanced kidney cancer: a systematic review and meta-analysis	**1. Fragestellung** the effect of antiangiogenic therapies on overall survival in mRCC patients
	2. Methodik ***Population*** mRCC patients ***Intervention*** anti-VEGF/VEGFR agent ***Komparator*** non anti-VEGF/VEGFR agent: treatment with placebo or interferon (IFN) ***Endpunkt*** Overall survival (OS) ***Suchzeitraum (Aktualität der Recherche)*** from January 2005 to July 2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt)*** 5 RCTs / 3469 Patienten ***Qualitätsbewertung der Studien*** Jadad seven-item scale

3. Ergebnisdarstellung

Studiencharakteristika und -qualität:

- All studies enrolled patients with clear-cell mRCC
- In all trials, patients were randomly allocated, all were phase III studies, three were double-blind trials.

Author	Year	Phase	Pts	Therapy		Jadad Score
				Experim.	Control	
Sternberg *et al.*	2013	3	435	Pazopanib	Pbo	5
Escudier *et al.*	2010	3	649	Beva+IFN	Pbo+ IFNα	5
Rini *et al.*	2010	3	732	Beva+IFN	IFNα	3
Motzer *et al.*	2009	3	750	Sunitinib	IFNα	3
Escudier *et al.*	2009	3	903	Sorafenib	Pbo	5

Wirksamkeit in Bezug auf den Endpunkt "Overall Survival"

Erstlinie

Subpopulation: treatment naïve patients

Treatment with the anti-VEGF/VEGFR agents decreased the risk of death (HR=0.88; 95%CI, 0.79 – 0.97; *p*=0.010) compared to control (control arm: 1,149 patients: 1,071 received IFN-alph and 78 received placebo). 4 RCT, 2364 patients; keine signifikante Heterogenität (Chi^2=1.31, p=0.73, I^2=0%).

No differences were found between the anti-VEGFR (TKIs) and the anti-VEGF agents (monoclonal antibody) in terms of the decrease in the risk of death (*p*=0.86).

Zweitlinie

keine Subgruppenanalyse durchgeführt

4. Fazit der Autoren

This study demonstrates that VEGF/VEGFR inhibition improves the overall survival in patients with metastatic clear-cell RCC. Its use as first line therapy is confirmed as the standard approach for patients in good and intermediate risk categories.

5. Hinweise durch die FB Med

In 1 der 4 RCT der Subgruppenanalyse mit „treatment naïve patients" wurde gegen Plazebo verglichen (Sternberg et al. 2013: Pazopanib vs. Plazebo): A total of 1,668 patients received control treatments with IFN-alpha (1,071 patients) or with placebo (597 patients).

Iacovelli R et al., 2014 [5]. Targeted therapies and complete responses in first line treatment of metastatic renal cell carcinoma. A meta-analysis of published trials	**1. Fragestellung** We performed a meta-analysis of published reports about antiangiogenic agents (AA) versus placebo or immunotherapy, focusing on the incidence rates and the relative risk of radiological complete response (CR) in mRCC.
	2. Methodik ***Population*** mRCC patients with good or intermediate prognosis ***Intervention*** Antiangiogenic agents (AAs) (sunitinib, sorafenib, pazopanib, and bevacizumab) as first line of therapy ***Komparator*** non-AAs: INF oder Plazebo ***Endpunkt*** complete response (CR) - Tumor response evaluations were based on Response Evaluation Criteria in Solid Tumors (RECIST) - Evaluated by investigator and/or independent imaging-review committee ***Suchzeitraum (Aktualität der Recherche)*** 01/2000 – 09/2012 ***Anzahl eingeschlossene Studien/Patienten (Gesamt)*** 5 RCT / 2747 Patienten ***Qualitätsbewertung der Studien*** Jadad Score
	3. Ergebnisdarstellung ***Quality of studies*** - For each patient, all imaging scans were evaluated by an independent imaging-review committee (IRC) blinded to study treatment, except for the bevacizumab trials.[5,6] In the latter, only the investigator assessment was performed. - Randomized treatment allocation sequences were generated in all trials. - Jadad' score was 3 for three studies and 5 for two studies (Table 1)

Table 1
Main characteristics of the included study.

Author	Year	Phase	Therapy	Control	Enrolled Pts	Evaluated Pts	Median age (years) Th/Ct	Median follow up (months) Th/Ct	Median treatment duration (months) Th/Ct	Median PFS (months) Th/Ct	Incidence of CR (%) AAs	95% CI	Control	95% CI	Jadad score
Escudier et al. [5]	2007	3	Beva + IFN	Pbo + IFN	641	595	61/60	13.3/12.8	9.7/5.1	10.2/5.4	1.3	0–2.7	2.1	0.3–3.9	5
Rini et al. [6]	2007	3	Beva + IFN	IFN	732	639	61/61	NA	6/3	8.5/5.2	3.4	1.3–5.5	1.3	0–2.7	3
Motzer et al. [7]	2007	3	Sunitinib	IFN	750	750	62/59	NA	6/4	11/5	3.3	1.2–5.3	1.2	0–2.6	3
Escudier et al. [8]	2009	2	Sorafenib	IFN	189	189	62/62.5	NA	6/5.5	5.7/5.6	0		1.1	0–3.7	3
Sternberg et al. [9]	2010	3	Pazopanib	Pbo	435	435	59/60	NA	7.4/3.8	9.2/4.2	0.3	0–1.2	0		5
Total					2747	2608					1.9	1.1–2.6	1.2	0.6–1.9	

Wirksamkeit in Bezug auf den Endpunkt "Complete Response"

- AAs vs. control: kein signifikanter Unterschied: RR of CR 1.52 (95% CI, 0.85–2.73; p = 0.16); keine signifkante Heterogenität (Q = 4.11; p = 0.39; I2 = 3%)
- Bevacizumab vs. control: kein signifikanter Unterschied: RR 1.28 (95% CI, 0.61–2.68; p = 0.52); keine signifkante Heterogenität (Q = 1.92; p = 0.17; I^2 = 48%)
- TKIs vs. control: kein signifikanter Unterschied: RR was 2.01 (95% CI, 0.77–5.25; p = 0.15); keine signifkante Heterogenität (Q = 1.57; p = 0.46; I^2 = 0.0%).

<u>Subgroup analysis by "prognosis"</u>
No relationships were found between the rates of CRs and the rate of patients with good prognosis (p = 0.27).

4. Anmerkungen/Fazit der Autoren

The introduction of AAs has significantly changed the life expectancy of patients with mRCC, as ORR and PFS have improved since these were introduced in clinical practice. Despite this activity, this meta-analysis suggests that CR is a rare event in mRCC and that AAs do not seem to influence CR rates and, accordingly, curability of this pathology.

5. Hinweise durch die FB Med

In 1 RCT wurde gegen Plazebo verglichen (Sternberg et al. [9] 2010: Pazopanib vs. Plazebo)→ Insgesamt in den 5 RCT: Patients in the control group had interferon (85%) or placebo (15%)

Systematische Reviews zur Zweitlinie nach Zytokin-Therapie

Albiges L et al., 2015 [1]. EAU – European Association of Urology	**1. Fragestellung** To systematically review relevant literature comparing the clinical effectiveness and harms of different sequencing and combinations of systemic targeted therapies for mRCC. The focus of this review is on both sequence and combination, and not on the results of front-line therapy clinical trials.
	2. Methodik

A Systematic Review of Sequencing and Combinations of Systemic Therapy in Metastatic Renal Cancer	***Population*** mRCC, keine näheren Angaben ***Intervention*** one of the prespecified systemic treatment agents, such as targeted, therapy, vaccines, chemotherapy, or cytokines ***Komparator*** any of the prespecified systemic therapy agents or placebo ***Endpunkt*** PFS, OS ***Suchzeitraum (Aktualität der Recherche)*** - the original EAU search was updated: January 2000 to September 2013 - methods protocol of the European Association of Urology (EAU) renal cell carcinoa 2013 guidelines was used as a basis for the search strategy ***Anzahl eingeschlossene Studien/Patienten (Gesamt)*** - n=24 RCTs (n= 9589 Patienten) für qualitative Betrachtung - n=4 für Metaanalyse ***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.

Wirksamkeit

Hinweis: Die Untersuchung der Wirksamkeit von Kombinationstherapien sowie die Meta-Analyse wurden nicht getrennt nach Erst- und Zweitlinie durchgeführt. Daher werden nur die Ergebnisse zur Therapiesequenz (nach Zytokin-Therapie – Table 1) ohne Vergleiche vs. Plazeob dargestellt:

Zweitlinie nach Zytokin-Therapie

- Axtinib ist vorteilhaft gegenüber Sorafenib in Bezug auf PFS (12.2 vs. 6.5 Monate)(1 Studie, n=251). P-Wert und Daten zu OS sind nicht angegeben.

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

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

- 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.
- Axitinib exhibited impressive PFS in cytokine pretreated patients in a phase 2 study that was confirmed in the phase 3 AXIS RCT [4] for the postcytokine subgroup with a PFS of 12.1 mo.
- Currently, use of cytokines is usually limited to countries where TKIs are not readily available or in a highly selected first-line population.
- Sunitinib, or other VEGF/VEGFR inhibiting therapies, have widely become the standard of care in the first-line setting.

5. Hinweise durch FB Med

- Fokus des Reviews lag auf Sequenz- und Kombinationstherapien.

	- In 4 der 5 Studien mit Patienten nach Zytokin-Therapie wurde ausschließlich gegen Plazebo oder Hormone verglichen. - Erstlinie: Der Review beinhaltete zudem 1 Studie mit der Population „non–clear cell renal cell carcinoma population (Erstlinie)“. Da in dieser unklar, welche Therapien verglichen wurden, wird diese nicht berichtet.

Leitlinien

Leitlinienprogramm Onkologie (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, Deutsche Krebsgesellschaft, Deutsche Krebshilfe), 2017 [9]. S3-Leitlinie Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms Version 1.2 – April 2017	**Fragestellung** Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms Schlüsselfragen zur systemischen Therapie in der metastasierten Situation - Welche Substanzen stehen in der first-line für die Behandlung des metastasierten Nierenzellkarzinoms zur Verfügung? Wie sind die Unterschiede in dieser Gruppe hinsichtlich des Überlebens und des Nebenwirkungsprofils? - 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? Sequenztherapie des klarzelligen Nierenzellkarzinoms Kombinationstherapie des klarzelligen Nierenzellkarzinoms

	Methodik
	<u>Grundlage der Leitlinie</u>
	- Vorversion aus 2015: Aktualisierung der Themen (Amendment)
	  - Systemtherapie des metastasierten klarzelligen Nierenzellkarzinoms
	  - Adjuvante Therapie
	- Fragestellungen definiert, konkretisiert und konsentiert durch die Leitliniengruppe am 29.10.2012.
	- Leitlinienadaption: Die Suche nach publizierten Leitlinien zu Diagnostik und Therapie des Nierenzellkarzinoms wurde im August 2012 durchgeführt und mittels DELBI Auswahl getroffen.
	- Systematische Literaturrecherchen: Direkte Vergleiche systemischer Therapien wurden durch das Department für Evidenzbasierte Medizin und Klinische Epidemiologie der Donau-Universität Krems durchgeführt; Literaturstellen wurden ausgewählt und mittels GRADE-Methodik bewertet.
	- Suchzeitraum: Januar 2013, erste Aktualisierungsrecherche: Januar

2014, Aktualisierungsrecherchen für das Amendment 2016: Januar/Juli 2016

- 3 Konsensuskonferenzen, finale schriftliche Abstimmung, DELPHI-Prozess

LoE: Verwendung nach Scottish Intercollegiate Guidelines Network (SIGN)

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

GoR

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

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

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.

Expertenkonsens (EK)

	Statements/Empfehlungen, für die eine Bearbeitung auf der Grundlage von Expertenkonsens (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. <u>Sonstige methodische Hinweise</u> - CoI dokumentiert und einsehbar - Suchstrategie veröffentlicht - Evidenztabellen einsehbar
	Empfehlungen **Chemotherapie des metastasierten klarzelligen Nierenzellkarzinoms** Beim metastasierten klarzelligen Nierenzellkarzinom soll eine palliative Chemotherapie nicht durchgeführt werden. (**GoR A, LoE 1++, Starker Konsens**) Jahr: 2015 Evidenzbasis: 281. Amato, R.J., *Chemotherapy for renal cell carcinoma.* Semin Oncol, 2000. **27**(2): p. 177-86. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/10768596 282. Motzer, R.J., et al., *Effect of cytokine therapy on survival for patients with advanced renal cell carcinoma.* J Clin Oncol, 2000. **18**(9): p. 1928-35. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/10784634 283. Buti, S., et al., *Chemotherapy in metastatic renal cell carcinoma today? A systematic review.* Anticancer Drugs, 2013. **24**(6): p. 535-54. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/23552469 **Immuntherapie des metastasierten klarzelligen Nierenzellkarzinoms** Beim metastasierten klarzelligen Nierenzellkarzinom soll eine alleinige Zytokintherapie basierend auf subkutanem IL-2 und/oder IFN nicht durchgeführt werden. (**GoR A, LoE 2++, Starker Konsens**) Jahr: 2015 Evidenzbasis: 285. Motzer, R.J., et al., Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med, 2007. 356(2): p. 115-24. PubMed: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17215529 286. Hudes, G., et al., Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med, 2007. 356(22): p. 2271-81. 287. Escudier, B., et al., Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet, 2007. 370(9605): p. 2103-11. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18156031 288. Rini, B.I., et al., Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol, 2008. 26(33): p. 5422-8. **Chemoimmuntherapie des klarzelligen Nierenzellkarzinoms** Beim metastasierten klarzelligen Nierenzellkarzinom soll eine Chemoimmuntherapie nicht durchgeführt werden. (**GoR A, LoE 1++, Starker Konsens**) Jahr: 2015 Evidenzbasis: 303. Gore, M.E., et al., Interferon alfa-2a versus combination therapy with interferon alfa-2a,

interleukin-2, and fluorouracil in patients with untreated metastatic renal cell carcinoma (MRC RE04/EORTC GU 30012): an open-label randomised trial. Lancet, 2010. **375**(9715): p. 641-8. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/20153039

Zielgerichtete Therapie des fortgeschrittenen und/oder metastasierten klarzelligen Nierenzellkarzinoms

Erstlinie

Tabelle 11: Systemtherapieoptionen gemäß Risikoprofil in der Erstlinientherapie

Therapielinie	Risikoprofil	Standard	Option
Erstlinie	Gut/intermediär	Bevacizumab + IFN Pazopanib Sunitinib	hochdosiertes IL-2
	Ungünstig	Temsirolimus	Pazopanib Sunitinib

Bei Patienten mit fortgeschrittenem und/oder metastasiertem klarzelligen Nierenzellkarzinom und niedrigem oder intermediärem Risiko sollen in der Erstlinientherapie Sunitinib, Pazopanib oder Bevacizumab + INF verwendet werden. (**GoR A, LoE 1++, Konsens**) Jahr: 2015

Evidenzbasis:
285. Motzer, R.J., et al., Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med, 2007. 356(2): p. 115-24. PubMed: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17215529
287. Escudier, B., et al., Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet, 2007. 370(9605): p. 2103-11. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18156031
302. Motzer, R.J., et al., Pazopanib versus sunitinib in metastatic renal-cell carcinoma. The New England journal of medicine, 2013. 369(8): p. 722-731. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/23964934

Bei Patienten mit fortgeschrittenem und/oder metastasiertem klarzelligen Nierenzellkarzinom und ungünstigem Risikoprofil soll in der Erstlinientherapie Temsirolimus verwendet werden. (**GoR A, LoE 1+, Konsens**) Jahr: 2015

Evidenzbasis:
286. Hudes, G., et al., Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med, 2007. 356(22): p. 2271-81.

Zweitlinie nach Zytokin-Therapie

Tabelle 12: Systemtherapieoptionen gemäß Vortherapie in der Zweitlinientherapie

Therapielinie	Vortherapie	Standard	Option
Zweitlinie	nach Zytokinen	Axitinib	Pazopanib Sorafenib

In der Zweitlinientherapie nach Sunitinib oder Zytokinen kann Axitinib verwendet werden. (**GoR 0, LoE 1+, Starker Konsens**) Jahr: 2017

Evidenzbasis:
323. 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. (**GoR 0, LoE 1+, Konsens**) Jahr: 2015

Evidenzbasis:
324. 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.
325. 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

Sequenztherapie des klarzelligen Nierenzellkarzinoms

Eine sequenzielle Therapie sollte nach Versagen oder Unverträglichkeit einer vorangegangenen Therapie angestrebt werden. Eine spezifische Sequenz von Substanzen kann nicht empfohlen werden. (**GoR B, LoE 1++, Konsens**) Jahr: 2015

Evidenzbasis:
327. 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.
332. 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.
349. Michel, M.S., et al., SWITCH: A randomized sequential open-label study to evaluate efficacy and safety of sorafenib (SO)/sunitinib (SU) versus SU/SO in the treatment of metastatic renal cell cancer (mRCC). J Clin Oncol (Meeting Abstracts), 2014. 32(4_suppl): p. 393-. PubMed: http://meeting.ascopubs.org/cgi/content/abstract/32/4_suppl/393

Kombinationstherapie des klarzelligen Nierenzellkarzinoms

Eine Kombinationstherapie mit zwei zielgerichteten Therapien soll derzeit nur innerhalb von klinischen Studien durchgeführt werdenmit Ausnahme der Kombination von Lenvatinib + Everolimus. (**GoR A, LoE 2+, Starker Konsens**) Jahr: 2017

Evidenzbasis
322. Motzer, R.J., 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. 16(15): p. 1473-82. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/26482279
351. Rini, B., et al., AMG 386 in combination with sorafenib in patients with metastatic clear cell carcinoma of the kidney: a randomized, double-blind, placebo-controlled, phase 2 study. Cancer, 2012. 118(24): p. 6152-61.
352. Negrier, S., et al., Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): a randomised phase 2 trial. Lancet Oncol, 2011. 12(7): p. 673-80. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/21664867
353. Ravaud, A., et al., Randomized phase II study of first-line everolimus (EVE)+ bevacizumab (BEV) versus interferon alfa-2a (IFN)+ BEV in patients (pts) with metastatic renal cell carcinoma (mRCC): record-2. Ann Oncol, 2012. 23.
354. Ravaud, A., et al., Randomized phase II study of first-line everolimus plus bevacizumab (E+B) versus interferon {alpha}-2a plus bevacizumab (I+B) in patients (pts) with metastatic renal cell carcinoma (mRCC): Record-2 final overall survival (OS) and safety results. ASCO Meeting Abstracts, 2013. 31(15_suppl): p. 4576. PubMed:

<table>
<tr><td></td><td>http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/4576
355. Rini, B.I., et al., Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. J Clin Oncol, 2014. 32(8): p. 752-9.
356. Fishman, M.N., et al., Phase Ib study of tivozanib (AV-951) in combination with temsirolimus in patients with renal cell carcinoma. Eur J Cancer, 2013. 49(13): p. 2841-50. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/23726267</td></tr>
<tr><td rowspan="2">National Comprehensive Cancer Network (NCCN), 2016 [12].

Kidney Cancer: NCCN Evidence Blocks Version 02.2017

Publikation: Motzer RJ et al.; 2017 [11].

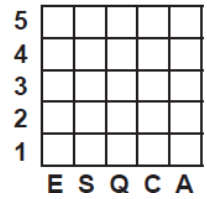
Kidney Cancer, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology</td><td>Zielsetzung
- Clinical Practice Guidelines in Oncology
- multidisciplinary recommendations for the clinical management of patients with clear cell and non–clear cell renal carcinoma</td></tr>
<tr><td>Methodik
<u>Grundlage der Leitlinie</u>
- Update der LL-Version 1.2017
- Updates mindestens jährlich geplant
- systematische Evidenzaufbereitung mit Konsensusprozessen -
- Suchzeitraum (Update): 07/15/15 - 07/15/16 in PubMed
<u>LoE / GoR</u>
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.

<u>Evidence Block</u>
Erklärung siehe Anhang Abbildung 1</td></tr>
</table>

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Sonstige methodische Hinweise

- CoI in der dazugehörigen Publikationen veröffentlicht
- Unklar, ob formalisierte Konsensusverfahren angewendet werden

Empfehlungen

Relapsed or Stage IV Disease and Surgically Unresectable Disease
Therapieschemata siehe **Anhang Abbildung 2 und Abbildung 3**

Erstlinie
First-line Therapy for Patients With Predominantly Clear Cell Carcinoma

Cytokine Therapy
High-dose IL-2: For highly selected patients* with relapsed or medically unresectable stage IV clear cell renal carcinoma, the NCCN panel lists high-dose IL-2 as a first-line treatment option with a **category 2A** designation.
*Patients with excellent performance status and normal organ function.

Targeted Therapy
Pazopanib: The NCCN panel has listed pazopanib as a **preferred category 1** option for first-line treatment of patients with relapsed or medically unresectable predominantly clear cell stage IV renal carcinoma.

Sunitinib: Based on these studies and its tolerability, the NCCN panel has also listed sunitinib as a **preferred category 1** option for first-line treatment of patients with relapsed or medically unresectable predominantly clear cell stage IV renal carcinoma.

Bevacizumab Along With Interferon: The NCCN panel recommends bevacizumab in combination with IFN-α as a **category 1** option for first-line treatment of patients with relapsed or medically unresectable predominantly clear cell stage IV renal carcinoma.

Temsirolimus: Based on these data, the NCCN panel has included temsirolimus as a **category 1** recommendation for first-line treatment of poor-risk patients with relapsed or medically unresectable predominantly clear cell stage IV renal carcinoma.

Sorafenib: The NCCN panel lists sorafenib as a **category 2A** option as first-line treatment for selected patients with relapsed or medically unresectable stage IV predominantly clear cell RCC.

Axitinib: Based on these results, the NCCN panel included axitinib as a first-line treatment option (**category 2A**).

Zweitlinie nach Zytokin-Therapie

Subsequent Therapy for Patients with Predominantly Clear Cell Carcinoma

Hinweis: In der Leitlinie wurden keine Empfehlungen explizit für Patienten nach Zytokin-Therapie gegeben. Daher werden hier die Empfehlungen gelistet, die auf Studien mit hauptsächlich Zytokin-vorbehandelten Populationen basieren.

Axitinib: In a phase II study of patients with cytokine-refractory metastatic RCC, the 5-year survival rate after treatment with axitinib was 20.6% (95% CI, 10.9%– 32.4%), with a median follow-up of 5.9 years.[139] Axitinib is listed as a **category 1** recommendation as a subsequent therapy option by the NCCN panel.

Referenzen

139. Rini BI, de La Motte Rouge T, Harzstark AL, et al. Five-year survival in patients with cytokine-refractory metastatic renal cell carcinoma treated with axitinib. Clin Genitourin Cancer 2013;11:107–114.

Sorafenib: [143] This study showed the effectiveness of sorafenib was primarily in patients whose disease 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.[144,145] Sorafenib is listed as a **category 2A** subsequent therapy option.

Referenzen

143. Escudier B, Eisen T, Stadler WM, 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;27:3312–3318.
144. Di Lorenzo G, Carteni G, Autorino R, et al. Phase II study of sorafenib in patients with sunitinib-refractory metastatic renal cell cancer. J Clin Oncol 2009;27:4469–4474.
145. Garcia JA, Hutson TE, Elson P, et al. Sorafenib in patients with metastatic renal cell carcinoma refractory to either sunitinib or bevacizumab. Cancer 2010;116:5383–5390.

Sunitinib: Sunitinib also has demonstrated substantial antitumor activity in the second-line therapy of metastatic RCC after progression on cytokine therapy.[111,146] Studies investigating the sequential use of sunitinib and sorafenib mostly are retrospective. There are prospective data, although limited, that suggest a lack of total cross resistance between TKIs, either sorafenib followed by sunitinib failures or vice versa—an observation that

	is consistent with their differences in target specificities and slightly different toxicity spectra that sometimes permit tolerance of one agent over another.[147–151] Sunitinib is considered a **category 2A** subsequent therapy option. Referenzen 111. Motzer RJ, Michaelson MD, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. J Clin Oncol 2006;24:16–24. 146. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. JAMA 2006;295:2516–2524. 147. Dudek AZ, Zolnierek J, Dham A, et al. Sequential therapy with sorafenib and sunitinib in renal cell carcinoma. Cancer 2009;115:61–67. 148. Eichelberg C, Heuer R, Chun FK, et al. Sequential use of the tyrosine kinase inhibitors sorafenib and sunitinib in metastatic renal cell carcinoma: a retrospective outcome analysis. Eur Urol 2008;54:1373–1378. 149. Sablin MP, Negrier S, Ravaud A, et al. Sequential sorafenib and sunitinib for renal cell carcinoma. J Urol 2009;182:29–34; discussion 34. 150. Shepard DR, Rini BI, Garcia JA, et al. A multicenter prospective trial of sorafenib in patients (pts) with metastatic clear cell renal cell carcinoma (mccRCC) refractory to prior sunitinib or bevacizumab [abstract]. J Clin Oncol 2008;26(Suppl):Abstract 5123. 151. Zimmermann K, Schmittel A, Steiner U, et al. Sunitinib treatment for patients with advanced clear-cell renal-cell carcinoma after progression on sorafenib. Oncology 2009;76:350–354. ***Pazopanib:*** The phase III trial comparing pazopanib with placebo, detailed earlier in “Pazopanib as First-line Therapy for Predominantly Clear Cell Carcinoma” (page 819) included 202 patients who received prior cytokine therapy. The average PFS in cytokine pretreated patients was 7.4 versus 4.2 months.[105] Based on these data, the NCCN panel considers pazopanib a **category 2A** subsequent therapy option. Referenzen 105. 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;28:1061–1068. ***Bevacizumab:*** Phase II trials have shown benefit of bevacizumab monotherapy after prior treatment with a cytokine.[154] Bevacizumab is a **category 2B** subsequent therapy option. Referenzen 154. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 2003;349:427–434. ***Temsirolismus:*** A phase II trial suggested benefit to temsirolimus therapy after prior treatment with a cytokine.[155] The NCCN panel considers temsirolimus a **category 2B** subsequent therapy option. Referenzen 155. Atkins MB, Hidalgo M, Stadler WM, et al. Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma.

	J Clin Oncol 2004;22:909–918. **High-dose IL-2** as subsequent therapy is listed as a subsequent therapy option for selected patients with excellent performance status and normal organ function (**category 2B).** _____ **Non–Clear Cell Carcinoma** <u>Systemic Therapy for Patients With Non–Clear Cell Carcinoma</u> ***Sunitinib*** is listed as preferred **category 2A** option for treatment-naïve patients with stage IV non– clear cell carcinoma. ***Temsirolimus*** is a **category 1** recommendation for patients with non–clear cell carcinoma with poor prognosis features (according to MSKCC risk criteria) and is a **category 2A** recommendation for patients belonging to other prognostic non–clear cell risk groups. ***Sorafenib*** is listed as a **category 2A** option for treatment-naïve patients with stage IV non–clear cell carcinoma. ***Pazopanib and Axitinib:*** Based on extrapolation, the NCCN panel has included these therapies as first-line therapy options for patients with relapsed or medically unresectable stage IV disease with non–clear cell histology (**category 2A**). ***Bevacizumab, Nivolumab*** The NCCN Guidelines include bevacizumab and the panel recently added nivolumab, cabozantinib, and lenvatinib plus everolimus as treatment options (**all category 2A**) for patients with non–clear cell carcinoma.
Ljungberg B et al., 2017, [10] European Association of Urology (EAU) Guidelines on renal cell carcinoma.	**Zielsetzung** clinical guidelines to provide urologists with evidence-based information and recommendations for the management of RCC
	Methodik <u>Grundlage der Leitlinie</u> - limited update of the 2016 publication - section “systemic therapy for metastatic disease”: this section was updated by a systematic review - Systematische Literaturrecherche, Identifkation und Priorsierung von Fragestellungen in Leitlinien-Panel, multidisziplinäres Panel - Peer Review: Chapter 7 ‘Disease management’ was peer reviewed prior to publication. Publications ensuing from SRs have all been peer reviewed. The other sections of the RCC Guidelines were peer reviewed prior to publication in 2015.

- Suchzeitraum (Update): July 2015 - June 2016

LoE / GoR (according to a modified GRADE methodology)

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 randomisation
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

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

Summary of Evidence (SOE) tables provided for each recommendation address a number of key elements:

1. the overall quality of the evidence which exists for the recommendation;
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ and is directional, either ‘do it’ (as represented by arrows pointing upwards) or ‘do not do it’ (arrows pointing downwards). The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Sonstige methodische Hinweise

- CoI dokumentiert und online einsehbar

Empfehlungen

Systemic therapy for advanced/metastatic RCC

Übersicht der Empfehlungen nach RCC-Typ und Risikogruppe in der Erstlinie, Zweitlinie (nach VEGF-Therapie) und Drittlinie **siehe Anhang Abbildung 4**

Immunotherapy in mRCC

Erstlinie

Empfehlungen

Recommendations	grade	
Do not offer monotherapy with interferon-α or high-dose bolus interleukin-2 as first-line therapy in metastatic RCC.	weak	↓

Summary of evidence

- Interferon-α monotherapy is inferior to VEG-targeted therapy or mTOR inhibition in mRCC. **(LoE 1b)**
- Interleukin-2 monotherapy may have an effect in selected cases (good PS [performance status] ccRCC, lung metastases only). **(LoE 2)**
- IL-2 has more side-effects than IFN-α. **(LoE 2)**
- High dose (HD)-IL-2 is associated with durable complete responses in a limited number of patients. However, no clinical factors or biomarkers exist to accurately predict a durable response in patients treated with HD-IL-2. **(LoE 1b)**
- Bevacizumab plus IFN-α is more effective than IFN-α treatment-naïve, low-risk and intermediate-risk ccRCC. **(LoE 1b)**
- Cytokine combinations, with or without additional chemotherapy, do not improve OS compared with monotherapy. **(LoE 1b)**

Evidenzbasis

356.Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomised controlled trial. Medical Research Council Renal Cancer Collaborators. Lancet, 1999. 353: 14. https://www.ncbi.nlm.nih.gov/pubmed/10023944
357.Motzer, R.J., et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol, 2002. 20: 289. https://www.ncbi.nlm.nih.gov/pubmed/11773181
358.Coppin, C., et al. Immunotherapy for advanced renal cell cancer. Cochrane Database Syst Rev, 2005: CD001425. https://www.ncbi.nlm.nih.gov/pubmed/15674877
359.Negrier, S., et al. Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial. Cancer, 2007. 110: 2468. https://www.ncbi.nlm.nih.gov/pubmed/17932908
360.Escudier, B., et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet, 2007. 370: 2103. https://www.ncbi.nlm.nih.gov/pubmed/18156031
361.Motzer, R.J., et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med, 2007. 356: 115. https://www.ncbi.nlm.nih.gov/pubmed/17215529
362.Hudes, G., et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med, 2007. 356: 2271. https://www.ncbi.nlm.nih.gov/pubmed/17538086
363.Rosenberg, S.A., et al. Prospective randomized trial of high-dose interleukin-2 alone or in conjunction with lymphokine-activated killer cells for the treatment of patients with advanced cancer. J Natl Cancer Inst, 1993. 85: 622. https://www.ncbi.nlm.nih.gov/pubmed/8468720

365.Fyfe, G., et al. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J Clin Oncol, 1995. 13: 688. https://www.ncbi.nlm.nih.gov/pubmed/7884429
366.McDermott, D.F., et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. J Clin Oncol, 2005. 23: 133. https://www.ncbi.nlm.nih.gov/pubmed/15625368
367.Yang, J.C., et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. J Clin Oncol, 2003. 21: 3127. ttps://www.ncbi.nlm.nih.gov/pubmed/12915604
369.Brahmer, J.R., et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med, 2012. 366: 2455. https://www.ncbi.nlm.nih.gov/pubmed/22658128
371.Motzer, R.J., et al. Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial. J Clin Oncol, 2015. 33: 1430. https://www.ncbi.nlm.nih.gov/pubmed/25452452

Systemic therapy in mRR

Erstlinie

Empfehlungen

Recommendations	grade	
Offer sunitinib or pazopanib as first-line therapy for metastatic clear-cell renal cell cancer (ccRCC).	strong	↑↑
Consider offering bevacizumab + Interferon (IFN)-α as first-line therapy for metastatic RCC in favourable and intermediate-risk ccRCC.	weak	↑
Consider offering temsirolimus as first-line treatment in poor-risk RCC patients.	weak	↑
Sunitinib can be offered as first-line therapy for non-clear cell mRCC.	weak	↑

Summary of evidence

- VEGF and TKIs increase PFS and/or OS as both first-line and second-line treatments for clear-cell mRCC. **(LoE 1b)**
- Sunitinib is more effective than IFN-α in treatment-naïve patients. **(LoE 1b)**
- Bevacizumab plus IFN-α is more effective than IFN-α in treatment-naïve low-risk and intermediate-risk patients. **(LoE 1b**)
- pazopanib is superior to placebo in both naïve mRCC patients and post-cytokine patients. **(LoE 1b)**
- First line pazopanib is not inferior to sunitinib in clear-cell mRCC patients.
- Temsirolimus monotherapy prolongs OS compared to IFN-α in poor-risk mRCC. **(LoE 1b)**
- Both mTOR inhibitors (everolimus and temsirolimus) and VEFG-targeted therapies (sunitinib or sorafenib) can be used in non-clear cell RCC. **(LoE 3)**
- No combination has proven to be better than single-agent therapy, with the exception of the combination of lenvatinib plus everolimus. **(LoE 1a)**

Evidenzbasis

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Systemic therapy in mRCC

Zweitlinie nach Zytokin-Therapie

Empfehlungen

Hinweis: Es sind keine Empfehlungen für Patienten nach Zytokin-Therapie enthalten.

Dazugehöriger Text zu: Treatment after progression of disease with cytokines

Trials have established sorafenib, axitinib and pazopanib as therapeutic options in this setting with a median PFS of 5.5, 12.1 and 7.4 months, respectively. Based on trial data, axitinib is superior to sorafenib in patients previously treated with cytokine therapy [389-391].

Referenzen

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	carcinoma: Updated results among cytokine-treated patients. J Clin Oncol 2012. J Clin Oncol 30, 2012 (suppl; abstr 4546). http://meetinglibrary.asco.org/content/94426-114 391.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: 552. https://www.ncbi.nlm.nih.gov/pubmed/23598172 <u>Summary of evidence</u> - 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)** - Pazopanib is superior to placebo in both naïve mRCC patients and post-cytokine patients. **(LoE 1b)** - Sorafenib has broad activity in a spectrum of settings in ccRCC patients previously treated with cytokine or targeted therapies. It is inferior to axitinib in both sunitinib or cytokine pre-treated patients. **(LoE 4)** <u>Evidenzbasis</u> 289.Kim EH, et al. Outcomes of laparoscopic and percutaneous cryoablation for renal masses. J Urol, 2013. 189: e492. [No abstract available]. 290.Goyal, J., et al. Single-center comparative oncologic outcomes of surgical and percutaneous cryoablation for treatment of renal tumors. J Endourol, 2012. 26: 1413. https://www.ncbi.nlm.nih.gov/pubmed/22642574 291.Zargar, H., et al. Cryoablation for Small Renal Masses: Selection Criteria, Complications, and Functional and Oncologic Results. Eur Urol, 2016. 69: 116. https://www.ncbi.nlm.nih.gov/pubmed/25819723 386.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: 1061. https://www.ncbi.nlm.nih.gov/pubmed/20100962
Hotte S et al., 2017 [4]. Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO) The use of targeted therapies in patients with inoperable locally advanced or metastatic renal cell	**Zielsetzung** The primary objective of this report is to determine the optimal targeted therapies for locally advanced or metastatic renal cell cancer (mRCC). A secondary objective is to determine whether a combination of agents is better than any single targeted agent. TARGET POPULATION: Adult patients with inoperable locally advanced or mRCC.
	Methodik <u>Grundlage der Leitlinie</u> - Update der Version von 2009 - Suche nach und Anpassung von existierenden Leitlinien - Systematische Literaturrecherche - interner und externer Review-Prozess - Suchzeitraum (Update): 2008 – April 2016 <u>LoE/GoR</u> - PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation.

cancer: updated guideline 2017	- Laut Handbuch (aber nicht konkret in der Leitlinie beschrieben): Each Working Group needs to arrive at a common interpretation of the available evidence as part of developing the recommendations. The PEBC has developed a set of criteria and questions to consider while interpreting the evidence, based on the GRADE methods and past experience. These criteria form an agenda for a discussion guided by the PEBC HRM. They are applied for each potential recommendation (or logical recommendation cluster or domain of the evidence). **Criteria** / **Questions** / **Judgements/Options** Type of Recommendation and Level of Obligation / At what level of obligation should the reader feel the recommended action should be followed? / ♦ Must (strong recommendation) ♦ Should ♦ May (weak recommendation or consensus statement) <u>Sonstige methodische Hinweise</u> - Empfehlungen mit Evidenz vernknüpft - Studienqualität bewertet, aber nicht mit der Empfehlung verknüpft - CoI offengelegt
	Empfehlungen **Erstlinie** **Either of the vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGF TKIs) sunitinib or pazopanib is recommended for previously untreated patients with locally advanced or mRCC.** <u>Qualifying Statements</u> Pazopanib and sunitinib have been shown to have similar survival benefits. However, sunitinib has been associated with more symptomatic side effects and pazopanib has been more frequently associated with hepatic toxicity. <u>Interpretation of Evidence for Recommendation</u> Sunitinib and pazopanib appear equally effective. Oncologists should discuss and assess the different toxicity profiles of the two drugs with their patients. <u>Key Evidence</u> 1. Larkin J, Paine A, Foley G, Mitchell S, Chen C. First-line treatment in the management of advanced renal cell carcinoma: Systematic review and network meta-analysis. Expert Opinion on Pharmacotherapy. 2015;16(12):1755-67. 2. Motzer RJ, Hutson TE, Olsen MR, Hudes GR, Burke JM, Edenfield WJ, et al. Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. Journal of Clinical Oncology. 2012;30(12):1371-7. 3. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013;369(8):722-31. 4. Escudier B, Porta C, Bono P, Powles T, Eisen T, Sternberg CN, et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES study. Journal of Clinical Oncology. 2014;32(14):1412-8.

Although bevacizumab combined with IFN-α is superior to IFN-α alone, it is not recommended due to a high rate of side effects. Current data do not support the use of single-agent bevacizumab, and it is not recommended.

Interpretation of Evidence for Recommendation

VEGF TKIs (sunitinib and pazopanib) are efficacious and safer alternatives to the bevacizumab plus INF-α combination.

Key Evidence

5. Escudier B, Bellmunt J, Negrier S, Bajetta E, Melichar B, Bracarda S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. Journal of Clinical Oncology. 2010;28(13):2144-50.
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Temsirolimus is a potential treatment option for first-line therapy for the subset of patients with poor-risk disease.

Qualifying Statements

Based on comparative results with another mammalian target of rapamycin (mTOR) inhibitor similar to temsirolimus (everolimus), VEGF TKI therapy is preferred for first- and subsequent-line therapies for all patient types.

Interpretation of Evidence for Recommendation

Temsirolimus or sunitinib are first-line treatment options for patients with poor-prognosis mRCC.

Key Evidence

8. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. New England Journal of Medicine. 2007;356(22):2271-81.
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Zweitlinie nach Zytokin-Therapie

Sorafenib is a treatment option in patients with favourable- to intermediate-risk RCC previously treated with cytokine therapies.

Interpretation of Evidence for Recommendation

Other therapies are preferred for first and subsequent lines for all patient

types.

Key Evidence

19.Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. Journal of Clinical Oncology. 2009;27(20):3312-8.
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Benahmed N et al., 2015 [2].

Belgian Health Care Knowledge Centre (KCE)

Renal cancer in adults: diagnosis, treatment and follow-up

Zielsetzung

Diagnosis, staging, treatment and follow-up of patients with confirmed renal cancer

2.3.3 Treatment of metastatic disease

Systemic therapy in first, second and third lines:

- Role of Interleukines;
- Role of targeted therapy;
- Sequencing.

Methodik

Grundlage der Leitlinie

- Clinical questions were developed in collaboration with members of the Guideline Development Group.
- Systematic review for a part of the clinical questions
- Collaboration between multidisciplinary groups of practising clinicians and KCE experts
- Critical appraisal with AGREE II, AMSTAR, QUADAS-2, Cochrane Collaboration's tool for assessing risk of bias
- Suchzeitraum: ≥ 2009-2014

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

Strength of each recommendation (SoR) was assigned using GRADE.

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

Erstlinie

Recommendations

Cytotoxic agents are not recommended in patients with clear cell metastatic renal cell carcinoma. (**SoR Strong, LoE High)**

Monotherapy with IFN-α or high-dose bolus IL-2 is not routinely be recommended as first-line therapy in metastatic renal cell carcinoma but can be used in selected patients. (**SoR Strong, LoE High)**

Sunitinib or Pazopanib is recommended as first-line therapy for clear cell metastatic renal celll carcinoma. (**SoR Strong, LoE Low)**

Bevacizumab + IFN-α is recommended as first-line therapy for metastatic renal cell carcinoma in favourable-risk and intermediate-risk clear-cell renal cell carcinoma. (**SoR Strong, LoE Moderate)**

Note : the conditions for a reimbursement by the health insurance are:
1) at least one grade 3 or 4 adverse event due to sunitinib;
2) the treatment with sunitinib was stopped for at least 4 weeks;

3) patient has no history of arterial thromboembolic disease or uncontrolled hypertension with standard treatment.
In addition, the reimbursement rule requires that treatment must be stopped in case of tumour progression assessed by CT-Scan or MRI after 8 weeks of treatment.

Temsirolimus is recommended as a first-line treatment in poor-risk renal cell carcinoma patients. (**SoR Strong, LoE Moderate)**

Schlussfolgerungen aus dem Review

- Chemotherapy and immunotherapy are inferior to targeted therapy in mRCC.
- Sunitinib (TKI) improves PFS and OS in comparison with IFN in CCmRCC patients.
- Sorafenib (TKI) does not improve PFS and ORR in comparison with IFN in low or intermediate risk CC mRCC patients.
- Temsirolimus (mTOR) improves PFS, OS and ORR in comparison with IFN in low or intermediate risk mRCC patients whatever the tumour type.
- The association of bevacizumab (monoclonal antibody) with IFN improves PFS and ORR in CC mRCC in comparison with IFN alone. However, there is no proven improvement in OS.
- Pazopanib does not improve PFS or OS in CC mRCC patients in comparison with Sunitinib. However, pazopanib improves ORR in CC mRCC patients.
- Addition of cytokines (IFN or IL-2) to Sorafenib does not improve PFS or OS in comparison with Sorafenib alone in mRCC whatever the tumour type.
- PFS, OS, ORR or QoL are not statistically significantly different when combination of targeted therapies (Temsirolimus + Bevacizumab) is compared with combination of monoclonal antibody (Bevacizumab) and IFN in mRCC whatever the level of risk and the tumour type.
- PFS and response rate are improved in CC mRCC patients treated with pazopanib in comparison to those treated with placebo. However, HRQoL did not improve.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Targeted therapies have a proven benefit in term of overall progression free survival, but with numerous side effects.
Quality of evidence	There is high-level evidence that shows the superiority of targeted therapies compared to immunotherapy. In addition, chemotherapy is inferior to immunotherapy. There is moderate evidence based on one study showing that sunitinib is superior to IFN in terms of progression free survival and overall survival. One study comparing pazopanib with sunitinib was downgraded for imprecision because confidence interval did not exclude a clinical important inferiority. There is moderate level of evidence that temsirolimus is superior to IFN based on one study of high quality. There is a high level of evidence that combination of bevacizumab + IFN is superior to IFN alone. However, a publication of Thompson et al. (2009) showed that sunitinib is superior to the combination of bevacizumab + IFN in terms of PFS.[111] Therefore, we downgraded to moderate level of evidence.
Costs (resource allocation)	In the comparison with sunitinib versus bevacizumab plus IFN, sunitinib presents lower cost than bevacizumab plus IFN. [111]

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	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 IL-2, Bevacizumab (10 mg/kg or 3 mg/kg) improves PFS and OS in CC mRCC patients in comparison with placebo. - 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. Evidenzbasis Sorafenib: 112. Escudier B, Eisen T, Stadler W, Szcylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356:125-34. 154. 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Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

- keine -

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 04.08.2017

#	Suchfrage
#1	MeSH descriptor: [Carcinoma, Renal Cell] explode all trees
#2	((renal and cell) or kidney* or nephroid* or hypernephroid* or grawitz* or collecting duct):ti,ab,kw
#3	(cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or sarcoma* or malign*):ti,ab,kw
#4	#2 and #3
#5	(hypernephroma* or rcc):ti,ab,kw
#6	#1 or #4 or #5
#7	#6 Publication Year from 2012 to 2017, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 04.08.2017

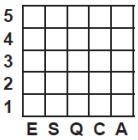
#	Suchfrage
#1	Search carcinoma, renal cell[MeSH Terms]
#2	Search ((renal[Title/Abstract] AND cell[Title/Abstract]) OR kidney*[Title/Abstract] OR nephroid*[Title/Abstract] OR hypernephroid*[Title/Abstract] OR grawitz*[Title/Abstract] OR collecting duct[Title/Abstract])
#3	Search (cancer*[Title/Abstract] OR tumor*[Title/Abstract] OR tumors[Title/Abstract] OR tumour*[Title/Abstract] OR neoplas*[Title/Abstract] OR carcinoma*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR sarcoma*[Title/Abstract] OR malign*[Title/Abstract])
#4	Search (#2) AND #3
#5	Search hypernephroma*[Title/Abstract] OR rcc[Title/Abstract]
#6	Search #1 OR #4 OR #5
#7	Search ((((((((((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 drug*[Title/Abstract]
#8	Search #6 AND #7
#9	Search "carcinoma, renal cell/therapy"[MeSH Terms]
#10	Search #8 OR #9
#11	Search (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
#12	Search ((((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])))

#	Suchfrage
#13	Search #11 OR #12
#14	Search #10 AND #13
#15	Search (#14) AND ("2012/08/01"[PDAT] : "2017/08/31"[PDAT])
#16	#15 NOT ("The Cochrane database of systematic reviews"[Journal])

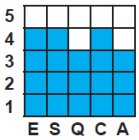
Leitlinien in Medline (PubMed) am 04.08.2017

#	Suchfrage
#1	Search carcinoma, renal cell[MeSH Terms]
#2	Search "Kidney Neoplasms"[Mesh:NoExp]
#3	Search ((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	Search (cancer*[Title/Abstract] OR tumor*[Title/Abstract] OR tumors[Title/Abstract] OR tumour*[Title/Abstract] OR neoplas*[Title/Abstract] OR carcinoma*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR sarcoma*[Title/Abstract] OR malign*[Title/Abstract])
#5	Search (#3) AND #4
#6	Search hypernephroma*[Title/Abstract] OR rcc[Title/Abstract]
#7	Search #1 OR #2 OR #5 OR #6
#8	Search (Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[Title] OR recommendation*[Title]) NOT (letter[ptyp] OR comment[ptyp]))
#9	Search #7 AND #8

Anhang



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Often provides long-term survival advantage or has curative potential
4	**Very effective:** Sometimes provides long-term survival advantage or has curative potential
3	**Moderately effective:** Modest, no, or unknown impact on survival but often provides control of disease
2	**Minimally effective:** Modest, no, or unknown impact on survival and sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal side effects. No interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only. Little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs is common
2	**Moderately toxic:** Significant toxicities often occur; life threatening/fatal toxicity is uncommon. Interference with ADLs is usual
1	**Highly toxic:** Usually severe, significant toxicities or life threatening/fatal toxicity often observed. Interference with ADLs is usual and/or severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** Several well-designed randomized trials
3	**Average quality:** Low quality randomized trials or well-designed non-randomized trials
2	**Low quality:** Case reports or clinical experience only
1	**Poor quality:** Little or no evidence

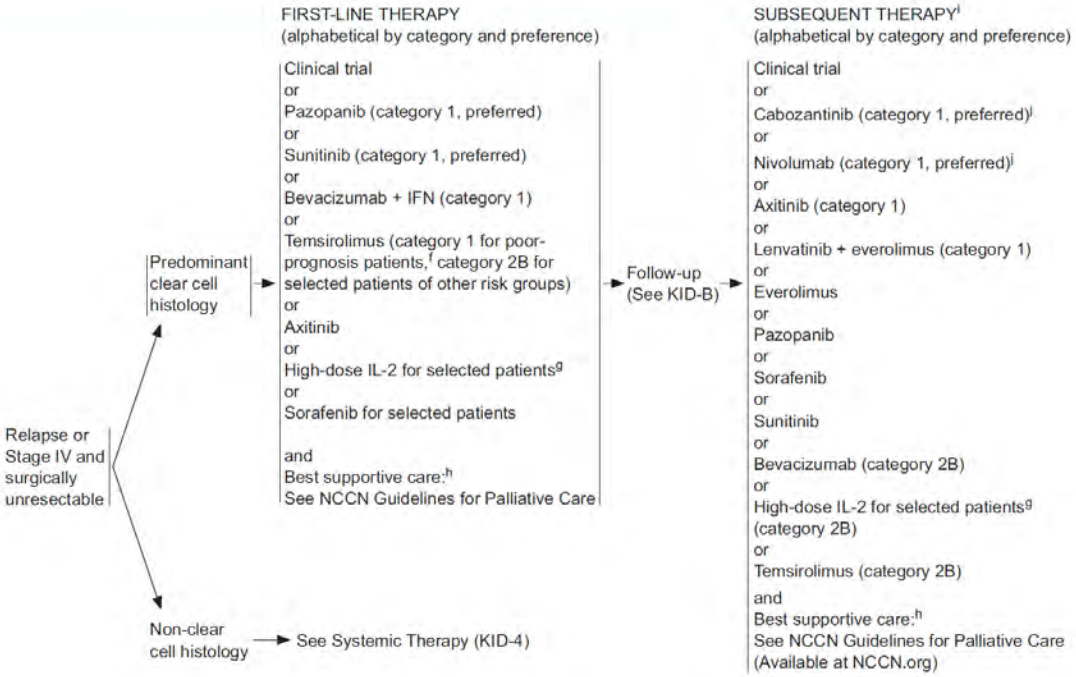
Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients; lower quality trials whether randomized or not
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

Abbildung 1 Definition Evidence Block, NCCN Clinical Practice Guidelines in Oncology[11,12]



[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.

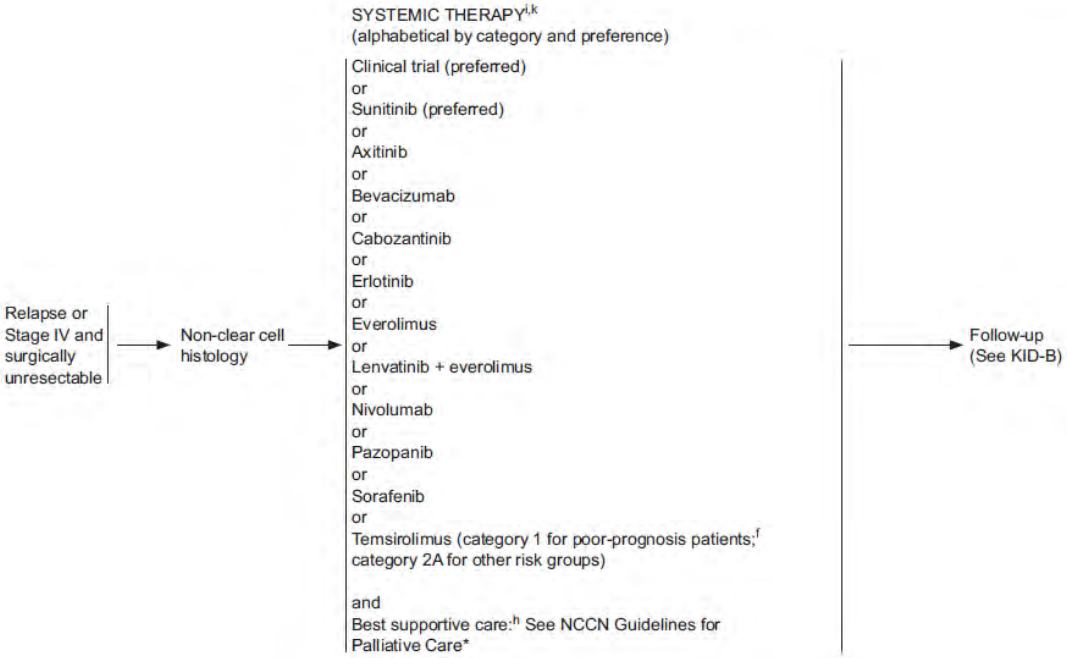
[h]Best supportive care can include palliative RT, metastasectomy, bisphosphonates, or RANK ligand inhibitors for bony metastases.

[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.

KID-3

Abbildung 2 Therapieschema – Predominantely clear cell histology, NCCN Clinical Practice Guidelines in Oncology[11,12]



*Available at NCCN.org

[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.

KID-4

Abbildung 3 Therapieschema – Non-clear cell histology NCCN Clinical Practice Guidelines in Oncology[11,12]

Table 7.3: EAU 2017 evidence-based recommendations for systemic therapy in patients with mRCC

RCC type	MSKCC risk group [356]	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 cabozantinib based on PFS: axitinib sorafenib# everolimus&	2b 2b 2b 2b 2b	after VEGF therapy: nivolumab cabozantinib everolimus& after VEGF and mTOR therapy: sorafenib after VEGF and nivolumab: cabozantinib axitinib everolimus	2b 2b 2b 1b 4 4 4	any targeted agent	4
Clear cell*	poor¶	temsirolimus sunitinib pazopanib	1b 2b 2b	any targeted agent	4				
Non-clear cell §	any	sunitinib	1b^^	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 cancer; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor.

*Doses: IFN-α - 9 MU three times per week subcutaneously, bevacizumab 10 mg/kg bi-weekly intravenously; sunitinib 50 mg daily orally for four weeks, followed by two 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 [356] 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 [391].

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

^^ Based on a SR [420].

Abbildung 4 Empfehlungen zur Therapie des mRCC der European Association of Urology (EAU) [10]

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