Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-B-030 Avelumab + Axitinib

Stand: April 2019

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

Avelumab in Kombination mit Axitinib
zur Erstlinien-Behandlung des fortgeschrittenen Nierenzellkarzinoms (RCC)

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	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: – Tivozanib: Beschluss vom 19. April 2018 – Cabozantinib: Beschluss vom 6. Dezember 2018 Arzneimittel-Richtlinie (AM-RL): Anlage VI – Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use), Stand: 7. Dezember 2017; Teil B: Wirkstoffe, die in zulassungsüberschreitenden Anwendungen (Off-Label-Use) NICHT verordnungsfähig sind: – Inhalatives Interleukin-2 (Proleukin®) zur Therapie des Nierenzellkarzinoms
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:	
Avelumab L01XC31 Bavencio®	Bavencio in Kombination mit Axitinib wird als Erstlinientherapie bei erwachsenen Patienten mit fortgeschrittenem Nierenzellkarzinom (RCC) angewendet (siehe Abschnitt 5.1).
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.
Nivolumab L01XC17 Opdivo®	OPDIVO ist in Kombination mit Ipilimumab für die Erstlinientherapie des fortgeschrittenen Nierenzellkarzinoms bei Erwachsenen mit intermediärem/ungünstigem Risikoprofil indiziert (siehe Abschnitt 5.1) […]
Tyrosin-Kinase-Inhibitoren	
Cabozantinib L01XE26 CABOMETYX™	CABOMETYX ist indiziert für die Behandlung des fortgeschrittenen Nierenzellkarzinoms (*renal cell carcinoma*, RCC): − bei nicht vorbehandelten Erwachsenen mit mittlerem oder hohem Risiko (siehe Abschnitt 5.1) − […]
Pazopanib L01XE11 Votrient®	<u>Nierenzellkarzinom (*renal cell carcinoma* – 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
Sorafenib L01XE05 Nexavar®	<u>Nierenzellkarzinom</u> Nexavar ist angezeigt zur Behandlung von Patienten mit fortgeschrittenem Nierenzellkarzinom, bei denen eine vorherige Interferon-alpha- oder Interleukin-2-basierte Therapie versagt hat oder die für solch eine Therapie nicht geeignet sind.
Sunitinib L01XE04 Sutent®	<u>Metastasierte Nierenzellkarzinome (mRCC)</u> SUTENT wird bei Erwachsenen zur Behandlung fortgeschrittener/ metastasierter Nierenzellkarzinome (mRCC) eingesetzt.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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®	Nierenzellkarzinom 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).
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: *[…]* − Fortgeschrittenes 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: 2019-B-030 (Avelumab+Axitinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	12. März 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DAHTA	DAHTA Datenbank
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

„Erstlinien-Behandlung des fortgeschrittenen Nierenzellkarzinoms (RCC) bei Erwachsenen.“

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Nierenzellkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 20.02.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1580 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 19 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2019 [4,5].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Cabozantinib (neues Anwendungsgebiet: Nierenzellkarzinom, Erstlinie) vom 06. Dezember 2018 und 21. Februar 2019

Beschluss vom: 06. Dezember 2018

Neues Anwendungsgebiet (laut Zulassung vom 8. Mai 2018)

CABOMETYX™ ist indiziert für die Behandlung des fortgeschrittenen Nierenzellkarzinoms (renal cell carcinoma, RCC) bei nicht vorbehandelten Erwachsenen mit mittlerem oder hohem Risiko.

a) Erwachsene Patienten mit nicht vorbehandeltem, fortgeschrittenem Nierenzellkarzinom mit mittlerem Risiko (IMDC-Score 1-2)

Zweckmäßige Vergleichstherapie

- Bevacizumab in Kombination mit Interferon alfa-2a

oder

- Monotherapie mit Pazopanib

oder

- Monotherapie mit Sunitinib

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Cabozantinib gegenüber Sunitinib:

Ein Zusatznutzen ist nicht belegt.

b) Erwachsene Patienten mit nicht vorbehandeltem, fortgeschrittenem Nierenzellkarzinom mit hohem Risiko (IMDC-Score ≥ 3)

Zweckmäßige Vergleichstherapie:

- Temsirolimus

oder

Sunitinib

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Cabozantinib gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

Beschluss vom: 21. Februar 2019

I. In Anlage XII werden die Regelungen unter Abschnitt II zur Geltungsdauer des Beschlusses über die Nutzenbewertung von Cabozantinib (neues Anwendungsgebiet: Nierenzellkarzinom, Erstlinie) vom 6. Dezember 2018 wie folgt geändert:

1. Die Angabe „1.“ wird gestrichen.

2. Der Satz „2. Die Geltungsdauer des Beschlusses ist nach Maßgabe der folgenden Regelung befristet: a) Die zu Patientengruppe b) „Erwachsene Patienten mit nicht vorbehandeltem, fortgeschrittenem Nierenzellkarzinom mit hohem Risiko (IMDC-Score ≥ 3)“ getroffenen Feststellungen in den Nummern 1, 2, 3 und 4 sind bis zum 6. Juni 2019 befristet.“ wird aufgehoben.

G-BA, 2018 [6].

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 – Tivozanib vom 19. April 2018.

Siehe auch IQWiG, 2018 [10]

Anwendungsgebiet (laut Zulassung vom 24.08.2017):

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.

a) Zur Erstlinientherapie von Patienten, mit günstiger oder intermediärer Prognose (MSKCC-Score 0-2)

Zweckmäßige Vergleichstherapie:

Bevacizumab in Kombination mit Interferon alfa-2a oder eine Monotherapie mit Pazopanib oder Sunitinib

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

b) Zur Erstlinientherapie von Patienten, mit ungünstiger Prognose (MSKCC-Score ≥3) Zweckmäßige Vergleichstherapie:

Temsirolimus

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

c) Bei Krankheitsprogression nach einer vorherigen Zytokin-Therapie, wenn noch nicht mit VEGFR- oder mTOR-Signalweginhibitoren behandelt wurde

Zweckmäßige Vergleichstherapie:

Axitinib oder Sorafenib

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Sorafenib:

Ein Zusatznutzen ist nicht belegt.

G-BA, 2018 [7].

Richtlinie des Gemeinsamen Bundesausschusses über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (Arzneimittel-Richtlinie/AM-RL). Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie: Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use), letzte Änderung in Kraft getreten am 19.01.2019. Teil B - Wirkstoffe, die in zulassungsüberschreitenden Anwendungen (Off-Label-Use) NICHT verordnungsfähig sind:

Inhalatives Interleukin-2 (Proleukin®) zur Therapie des Nierenzellkarzinom

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G-BA, 2009 [3].

Beschluss des Gemeinsamen Bundesausschusses über die 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; vom 15. Oktober 2009.

Der Gemeinsame Bundesausschuss hat in seiner Sitzung am 15. Oktober 2009 beschlossen, den Auftrag an die Expertengruppe Off-Label im Fachbereich Onkologie zur Erstellung einer Bewertung zum Stand der wissenschaftlichen Erkenntnis über die Anwendung von

Interferon alpha und Interleukin-2-basierte Immunochemotherapien beim metastasierten Nierenzellkarzinom und in der adjuvanten Therapie zurückzunehmen.

3.2 Cochrane Reviews

Unverzagt S et al., 2017 [15].

Immunotherapy for metastatic renal cell carcinoma (Review).

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.

Methodik

Population:

- Participants diagnosed with all types of histologically confirmed mRCC including stage IV (T4 any N M0, any T any N M1)

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).

Endpunkt:

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).

Recherche/Suchzeitraum:

- bis 10/2016

Qualitätsbewertung der Studien:

- Cochrane's 'Risk of bias' assessment tool
- quality of evidence using GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

8 RCTs/quasi-RCTs, 4732 participants

Charakteristika der Population:

- We excluded studies that focused on patients with locally advanced disease.

Qualität der Studien:

Studienergebnisse:

First-line therapy (in previously untreated patients)

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

Anmerkung/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.

Kommentare zum Review: Patientenpopulation mit metastasiertem Nierenzellkarzinom.

3.3 Systematische Reviews

Wang HT et al., 2019 [17].

A meta-analysis of efficacy and safety of sorafenib versus other targeted agents (TAs) for metastatic renal cell carcinoma (mRCC)

Fragestellung

We performed a meta-analysis of studies to evaluate the therapeutic effect and adverse effects of sorafenib compared to other TAs in the treatment of mRCC.

Methodik

Population:

- Patients with mRCC and/or patients with advanced RCC

Intervention:

- Sorafenib

Komparator:

- TA-based chemotherapy (Sunitinib, Axitinib, IFN-2A, Tivozanib)

Endpunkte:

- PFS
- OS
- Overall response rate (ORR)
- SAE rate

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane Library up to September 2017

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 trials
- 3 RCTs, 2 trials retrospektive study design

Charakteristika der Population:

- k.A.

Qualität der Studien:

- All included studies in this study were based on moderate- to high-quality evidence.

Studienergebnisse:

- Progression-free survival

  - Pooled PFS data from all 5 studies[18–22] showed that other TAs prolonged PFS (OR=0.78, 95%CI=0.70–0.86, P<.001) compared with the chemotherapy group
- Overall survival
  - The pooled data showed that sorafenib plus chemotherapy did not improve OS (OR=0.97, 95%CI=0.78– 1.22, P=.82) when compared with other TA treatments
- Overall response rate
  - The pooled ORR data did achieve advantage in the other TAs (OR=1.89, 95%CI=1.38–2.59, P<.0001). In other words, the addition of sorafenib did not increase the rate of ORR
- AEs
  - Only 2 studies reported available data on AEs so it was not possible to perform meta-analysis

Anmerkung/Fazit der Autoren

Sorafenib did not achieve efficacy and safety benefit in patients with mRCC compared with those treated with TAs. The role of sorafenib in first-line treatments of mRCC may change in favor of newer drugs. More research is needed to confirm whether these new TAs could replace sorafenib as the gold standard in the future.

Kommentare zum Review: 2 von 5 eingeschlossenen RCTs haben ein retrospektives Studiendesign

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Iacovelli R et al., 2018 [9].

Immunotherapy versus standard of care in metastatic renal cell carcinoma. A systematic review and meta-analysis

Fragestellung

We aim to perform a systematic review and meta-analysis of the randomized trials comparing immune checkpoint inhibitors over anti-VEGF/ VEGFRs agents in order to better define the role of this novel strategy for treatment of mRCC, as well as the predictive role of PD-L1 expression in patients receiving immunotherapy.

Methodik

Population:

- mRCC patients

Intervention:

- anti-PD-1/PD-L1 immune checkpoint inhibitor

Komparator:

- sunitinib or everolimus

Endpunkte:

- OS
- PFS

- overall response rate (ORR)

Recherche/Suchzeitraum:

- MEDLINE/PubMed, Cochrane Library and the abstracts presented at the American Society of Clinical Oncology (ASCO) conferences for citations until April 2018.

Qualitätsbewertung der Studien:

- Jadad 5-item scale
- Data extraction according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement

Ergebnisse

Anzahl eingeschlossener Studien:

- 4, Three out of four were randomized phase III trials and one was a randomized phase II study [13-16]

Charakteristika der Population:

- Three studies enrolled treatment naïve patients while one included patients previously treated with anti-VEGFRs TKIs

Qualität der Studien:

- All the studies included in this meta-analysis were randomized clinical trials, and all were unblinded. The Jadad's score was evaluated only for the two published studies [14,15] and, in these cases, it was 3 for both of them. It was impossible to calculate the Jadad's score for the remaining two studies [13,16], not yet published at the time of the analysis.

Table 1
Main characteristics of the included studies.

Study	Line of therapy	Exp arm (Pts N°)	Ctr arm (Pts N°)	Population	OS		PFS		ORR		Jadad's score
					HR	95%CI	HR	95%CI	n/tot	n/tot	
CheckMate025	Second	Nivolumab (410)	Everolimus (411)	All	0.74	0.63 –0.88	0.85	0.73–0.99	103/410	22/411	3
				All PD-L1 + (22.0%)	0.79	0.53–1.17	NA	NA	NA	NA	
CheckMate214	First	Nivolumab Ipilimumab (550*)	Sunitinib (546*)	All	0.68	0.49–0.95	0.98	0.79–1.23	215/550	175/546	3
				All PD-L1 + (24.1%) (poor/int group)	0.45	0.29–0.71	0.46	0.31–0.67	58/100	25/114	
IMmotion150	First	Atezolizumab Bevacizumab (101)	Sunitinib (101)	All	NA	NA	0.88	0.64–1.22	35/101	33/101	NA
				All PD-L1 + (54.5%)	NA	NA	0.60	0.38–0.94	24/50	17/60	
IMmotion151	First	Atezolizumab Bevacizumab (454*)	Sunitinib (461*)	All	0.81	0.63–1.03	0.88	0.74–1.04	150/454	143/460	NA
				All PD-L1 + (39.6%)	0.68	0.46–1.0	0.93	0.72–1.21	64/178	61/184	

Legend: * = Intention to treat population; CI = confidence interval; HR = hazard ratio; int = intermediated; N° = number; NA = not available; ORR = overall response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival, Pts = patients, Exp = experimental, Ctr = control.

Studienergebnisse:

- Two studies compared combination of atezolizumab plus bevacizumab to sunitinib in first-line of therapy [13, 16]
- One study compared the combination of nivolumab plus ipilimumab to sunitinib in first-line of therapy [15]
- Total of 2832 patient were available for evaluation of OS while 3033 were evaluable for PFS and ORR

- Overall survival - treatment naïve patients: immunotherapy was able to decrease the risk of death over sunitinib by 24% (HR=0.76; 95%CI, 0.62–0.93; p < 0.001)
- PFS - treatment naïve patients: no significant improvement in PFS in favor of immunotherapy over sunitinib was found
- ORR - treatment naïve patients: immunotherapy was able to increase the relative risk of response over sunitinib in first-line by 14% (RR=1.14; 95%CI, 1.02–1.28; p=0.03). Again, no significant heterogeneity was found (Chi2=1.34, p=0.51; I2=0%)

Anmerkung/Fazit der Autoren

In conclusion, our analysis confirmed that immunotherapy improved OS when compared to standard of care for treatment of mRCC. This benefit was especially confirmed in the first-line setting, when immunotherapy was compared to sunitinib. Our data also suggested caution with the use of PFS as endpoint for study design and interpretation, even when the analysis was restricted to patients with PD-L1 positive tumors. Mature clinical data of available studies, other than standardized evaluation of the PD-L1 expression, as well as new results from ongoing clinical trials might improve our knowledge relative to the use of immunotherapy in mRCC in next future.

Kommentare zum Review: Qualitätsbewertung Jadad-Score 3 nur für eine relevante Studie verfügbar [15]

Referenzen
[13] McDermott DF, Atkins MB, Motzer RJ, Rini BI, Escudier BJ, Fong L, et al. A phase II study of atezolizumab (atezo) with or without bevacizumab (bev) versus sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC) patients (pts). J Clin Oncol 2017;35(6_suppl):431.
[14] Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373(19):1803–13.
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Schmidt E et al., 2018 [14].

Cabozantinib versus Standard-of-Care Comparators in the Treatment of Advanced/Metastatic Renal Cell Carcinoma in Treatment-naïve Patients: a Systematic Review and Network Meta-Analysis.

Fragestellung

To indirectly assess efficacy of cabozantinib versus standard-of-care (SoC) comparators in the first-line treatment of aRCC.

Methodik

Population:

- adult patients ≥ 18 years of age with previously untreated aRCC.

Intervention:

- cabozantinib

Komparator:

- standard-of-care (SoC)

Endpunkte:

- overall survival (OS) and progression-free survival (PFS)

Recherche/Suchzeitraum:

- 07/2017

Qualitätsbewertung der Studien:

- The study quality of selected studies was systematically appraised using the NICE checklist

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 studies

Charakteristika der Population:

- The overall study populations were heterogeneous in terms of risk groups; some studies included favorable risk patients.
- patients had similar median age (~ 60 years), and most of the patients included in the studies were male

Qualität der Studien:

- studies were mostly considered to be of good quality, while a frequent source of potential bias was open-label design, which was reduced by involving an independent imaging-review committee in some of the studies.

Studienergebnisse:

- In intermediate-risk patients, HRs (95% confidence interval) for PFS were 0.52 (0.33, 0.82), 0.46 (0.26, 0.80), 0.20 (0.12, 0.36), and 0.37 (0.20, 0.68) when cabozantinib was compared with sunitinib, sorafenib, interferon (IFN), or bevacizumab plus IFN, respectively.
- In poor-risk patients, the NMA also demonstrated significant superiority in terms of PFS for cabozantinib; HRs were 0.31 (0.11, 0.90), 0.22 (0.06, 0.87), 0.16 (0.04, 0.64), and 0.20 (0.05, 0.88), when cabozantinib was compared with sunitinib, temsirolimus, IFN, or bevacizumab plus IFN, respectively.
- When the overall study populations were compared, the results were similar to the subgroup analyses. OS HRs in all analyses favored cabozantinib, but were not statistically significant.

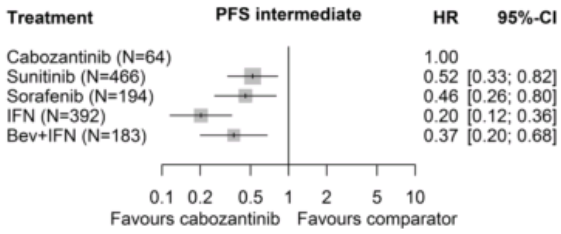


Fig. 2 PFS network meta-analysis forest plots — intermediate-risk group *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: Interferon; *PFS*: progression-free survival

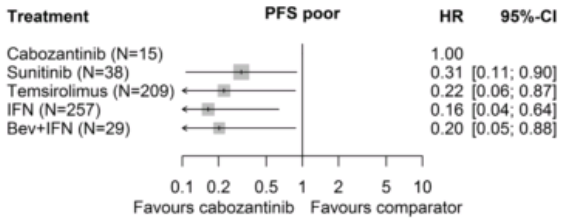


Fig. 3 PFS network meta-analysis forest plots — poor risk-group *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *PFS*: progression-free survival

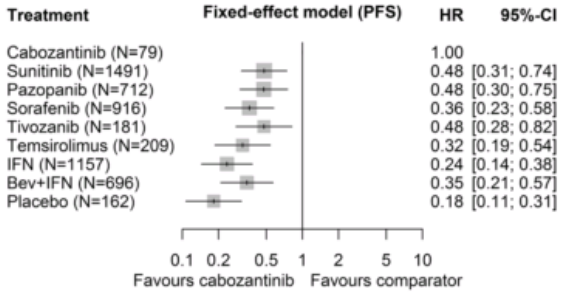


Fig. 4 PFS network meta-analysis forest plots — overall-risk group *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *PFS*: progression-free survival

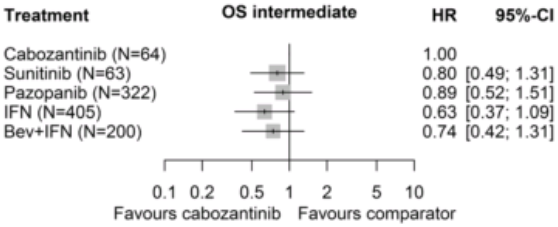


Fig. 5 OS network meta-analysis forest plots — intermediate-risk group. *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *OS*: overall survival

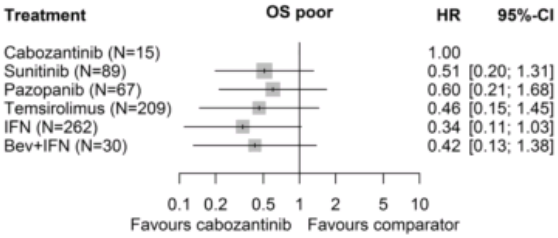


Fig. 6 OS network meta-analysis forest plots — poor-risk group. *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *OS*: overall survival

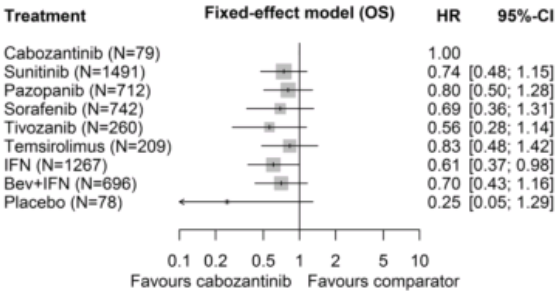


Fig. 7 OS network meta-analysis forest plots — overall-risk group. *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *OS*: overall survival

Anmerkung/Fazit der Autoren

The results suggest that cabozantinib significantly increases PFS in intermediate-, and poor-risk subgroups when compared to standard-of-care comparators. Although overall populations included favorable risk patients in some studies, the results seen were consistent with the subgroup analyses.

Kommentare zum Review: Patientenpopulation beinhaltet fortgeschrittenes/metastasiertes Nierenzellkarzinom.

Wallis CJD et al., 2018 [16].

First-line Systemic Therapy for Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis

Fragestellung

To indirectly compare the efficacy and safety of systemic therapies used in the first-line treatment of mRCC

Methodik

Population:

- Patients with metastatic RCC

Intervention und Komparator:

- Sunitinib, Nivolumab, Ipilimumab, Cabozantinib, Atezolizumab, Bevacizumab, Sorafenib, Tivozanib, Pazopanib, and Everolimus

Endpunkte:

- PFS (primary outcome)
- OS and grade 3 and 4 adverse events (AEs) (secondary outcomes)

Recherche/Suchzeitraum:

- Medline, EMBASE, Web of Science, and Scopus databases were searched using the OvidSP platform for studies indexed from database inception to October 23, 2017

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- SR: 37 trials reporting on 13.128 patients
- NMA: 10 trials reporting on 4819 patients

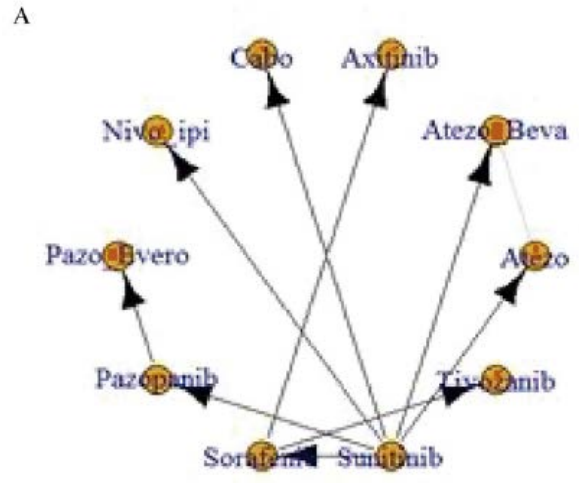


Fig. 2 – Analysis of progression-free survival: (A) network diagram; (B) forest plot, with sunitinib as the comparator; (C) forest plot, with cabozantinib as the comparator; (D) SUCRA plot.
Atezo = atezolizumab; Atezo_Beva = atezolizumab + bevacizumab; Cabo = cabozantinib; CrI = credible interval; Nivo_Ipi = nivolumab + ipilimumab; Pazo_Evero = pazopanib + everolimus.

A

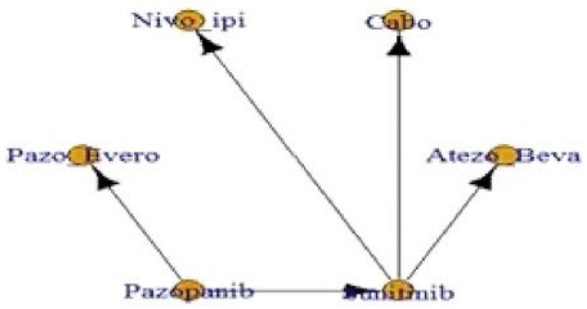


Fig. 3 – Analysis of overall survival: (A) network diagram; (B) forest plot, with sunitinib as the comparator; (C) forest plot, with nivolumab plus ipilimumab as the comparator; (D) SUCRA plot.
Atezo_Beva = atezolizumab + bevacizumab; Cabo = cabozantinib; CrI = credible interval; Nivo_Ipi = nivolumab + ipilimumab; Pazo_Evero = pazopanib + everolimus.

Charakteristika der Population:

- predominately male populations with a median age in the 60s

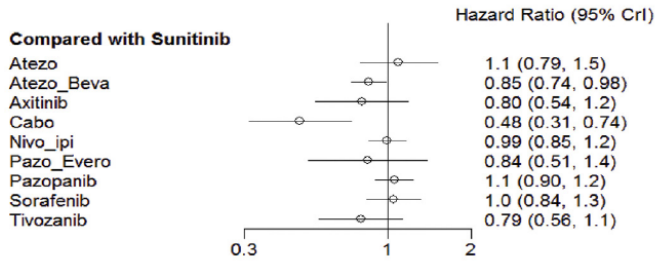
Qualität der Studien:

- K.A.

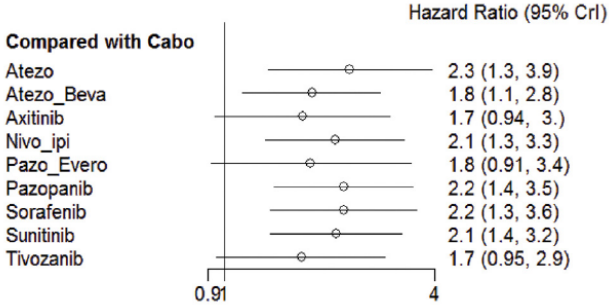
Studienergebnisse:

- PFS
  - ten trials comparing ten different treatments (4819 total patients)
  - Compared to treatment with sunitinib, PFS differed in a significant manner only for those patients who received cabozantinib (HR: 0.48, 95% CrI: 0.31–0.74). When compared to cabozantinib, all other treatments had significantly worse PFS except axitinib, pazopanib alternating with everolimus, and tivozanib.

B

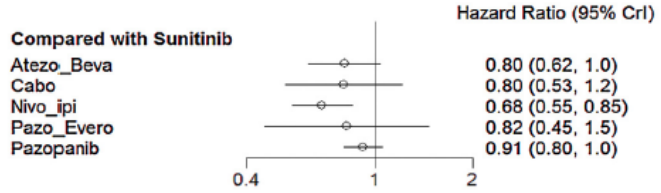


C



- Overall survival
  - five trials comparing sunitinib, cabozatinib, nivolumab plus ipilimumab, atezolizumab plus bevacizumab, pazopanib, and pazopanib plus everolimus (3379 total patients).
  - Compared to sunitinib, only nivolumab plus ipilimumab was associated with a significantly lower risk of overall mortality (HR: 0.68, 95% CrI: 0.55–0.85).
  - On indirect comparison, there was no difference in OS between nivolumab plus ipilimumab and cabozantinib (HR: 1.2, 95% CrI: 0.73–1.9) or atezolizumab plus bevacizumab (HR: 1.2, 95% CrI: 0.84–1.6).

B



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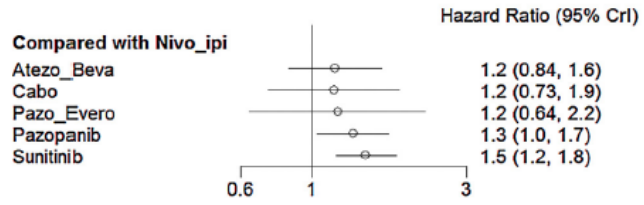

- Sensitivity analysis
  - sensitivity analysis for PFS and OS assessing only patients with intermediate- and high-risk disease.
  - included two studies assessing nivolumab plus ipilimumab, cabozantinib, each compared to sunitinib
  - SUCRA (surface under the cumulative ranking curves) based analysis: there was a 99% probability that cabozantinib was the preferred choice for PFS and an 85% probability that nivolumab plus ipilimumab was the preferred choice for OS
- Adverse events
  - Compared to sunitinib, nivolumab plus ipilimumab (OR: 0.52, 95% CrI: 0.41–0.66), and atezolizumab plus bevacizumab (OR: 0.57, 95% CrI: 0.44–0.74) were associated with a significantly lower likelihood of toxicity

Fazit der Autoren

In this systematic review and network meta-analysis of first-line systemic therapy for patients with mRCC, utilizing indirect comparison of data from phase 2 and 3 clinical trials, cabozantinib was identified as being highly likely to provide the greatest PFS benefit, while nivolumab plus ipilimumab was most likely to provide the greatest OS benefit. Furthermore, nivolumab plus ipilimumab was likely to be the best tolerated regime.

Wei C et al., 2018 [19].

Efficacy of targeted therapy for advanced renal cell carcinoma: a systematic review and meta-analysis of randomized controlled trials.

Fragestellung

We conducted a systematic review and meta-analysis of the literature on the efficacy of the targeted therapies in the treatment of advanced RCC and, via an indirect com-parison, to provide an optimal treatment among these agents.

Methodik

Population:

- patients with advanced RCC

Intervention/ Komparator:

- Targeted therapies via an indirect comparison

Endpunkte:

- progression free survival (PFS)
- overall survival (OS)
- objective response rate (ORR)

Recherche/Suchzeitraum:

- 01/2015

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 30 studies

Charakteristika der Population:

- Patients of any age, sex, or mRCC stage

Qualität der Studien:

- twenty-four studies scored a 5 because the description of randomization and technique was adequate.
- the other six studies scored a 3 on the Jadad scale because the description of double-blind or the method of blinding was inappropriate

Studienergebnisse:

VEGF(r)-TKI & mTOR inhibitor vs placebo

- Compared with placebo, VEGF(r)-TKI & mTOR inhibitor were associated with improved PFS (HR: 0.45; 95% CI: 0.40-0.51; P<0.001), improved OS (HR: 0.88; 95% CI, 0.78-1.00; P=0.05) and higher ORR (RR: 2.21; 95% CI, 1.53-3.91; P<0.001)

VEGF(r)-TKI & mTOR inhibitor vs IFN-α

- Compared with IFN-α, VEGF(r)-TKI & mTOR inhibitor were associated with improved PFS (HR: 0.62; 95% CI, 0.57-0.68; P<0.001) improved OS (HR: 0.80; 95% CI, 0.70-0.91; P<0.001) and higher ORR (RR: 2.30; 95% CI, 1.83-2.90; P<0.001)

Efficacy of sorafenib and BEV + IFN-α

- Three trials compared sorafenib combination vs sorafenib; there was no signifi cant difference with regard to PFS and OS, but with a higher ORR
- Three trials compared single or combination VEGF(r)- -TKI & mTOR inhibitor vs BEV + IFN-α; there was no significant difference with regard to PFS, OS, or ORR

Anmerkung/Fazit der Autoren

Our data suggest that targeted therapy with VEGF(r)-TKI & mTOR inhibitor is associated with superior efficacy for treating advanced RCC with improved PFS, OS and higher ORR compared to placebo and IFN-α. Agents targeting VEGF and mTOR pathways improve PFS in both first-line and second-line settings. In the light of this available evidence, there is no statistically significant PFS difference between BEV+IFN and TKIs in first-line mRCC therapy.

In summary, here we give a comprehensive overview of current targeted therapies of advanced RCC that may provide evidence for the adequate targeted therapy selecting.

Kommentare zum Review: Patientenpopulation beinhaltet fortgeschrittenes/metastasiertes Nierenzellkarzinom, Erst- und Zeitlinienbehandlung.

Rousseau B et al., 2016 [13].

First-line antiangiogenics for metastatic renal cell carcinoma: A systematic review and network meta-analysis.

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.

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.

Recherche/Suchzeitraum:

- bis 07/2014

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Netzwerk-Metaanalyse

- Bayesian hierarchical model. This model incorporates heterogeneity between multiple trials of the same pair of treatments and adds a random effect for each treatment pair to allow for inconsistency in the model.

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 RCTs / 4.282 patients (19 treatment arms in network meta-analysis)

Charakteristika der Population:

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.

Qualität der Studien:

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

Studienergebnisse:

Wirksamkeit

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

Progression-free survival

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).

Overall survival

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, I2= 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, I2= 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; I2= 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 treatments

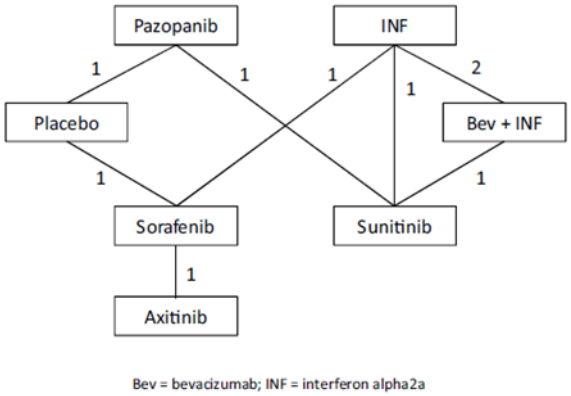

Fig. 3. Network of treatment comparisons established for the nine selected two-arm clinical trials. Lines between agents represent direct comparisons. The numbers represent the number of trial arms providing direct comparison between the angiogenic agents. Bev = bevacizumab; INF = interferon alpha2a.

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).

1-year survival

- 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).

Objective response rate and disease control rate

- 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.

Safety

permanent treatment discontinuations:

- 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.

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.

Kommentare zum Review: Das Fazit bezüglich der Vergleiche zwischen den einzelnen antiangiogenetischen Substanzen beruht auf den indirekten Vergleichen der Netzwerk-Metaanalyse. Patientenpopulation mit metastasiertem Nierenzellkarzinom.

Wang L et al., 2015 [18].

Therapeutic effects and associated adverse events of first‐line treatments of advanced renal cell carcinoma (RCC): a meta‐analysis.

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.

Methodik

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

Recherche/Suchzeitraum:

- bis 10/2014

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

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTs / 2736 Patienten

Charakteristika der Population:

- Keine näheren Angaben

Qualität der Studien:

- moderate quality of the included trials

Table 1 Summary of trails involved

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)

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

Studienergebnisse:

Wirksamkeit gegenüber INF

Tumor progression

- signifkanter Vorteil von sorafenib (1 RCT; n=189), sunitinib (1 RCT, 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%

Objective response rate (ORR)

- 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%

Disease control rate (DCR)

- 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%

Median progression-free survival

- 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%

Median overall survival

- 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%

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.

Kommentare zum Review: Aussage/Fazit zum Vergleich von Bevacizumab+IFN vs Sorafenib, Sunitinib oder Temsirolimus beruht aus indirekten Vergleichen der Effektschätzer (siehe forest plots).

3.4 Leitlinien

Gallardo E et al., 2018 [2].

SEOM (Spanish Society of Medical Oncology) and SOGUG (Spanish Oncology Genitourinary Group)

SEOM clinical guideline for treatment of kidney cancer (2017).

Fragestellung

The goal of this article is to provide recommendations about the management of kidney cancer.

Methodik

Grundlage der Leitlinie

The SEOM guidelines have been developed with the consensus of ten genitourinary cancer oncologists from SEOM (Spanish Society of Medical Oncology) and SOGUG (Spanish Oncology Genitourinary Group).

Recherche/Suchzeitraum:

- k.A.

LoE/GoR

Levels of evidence

- I Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
- II Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
- III Prospective cohort studies
- IV Retrospective cohort studies or case–control studies
- V Studies without control group, case reports, experts opinions

Grades of recommendation

- A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
- B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
- C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages; optional
- D Moderate evidence against efficacy or for adverse outcome, generally not recommended
- E Strong evidence against efficacy or for adverse outcome, never recommended

Empfehlungen

First-line treatment in advanced disease

- In patients with good or intermediate prognosis, sunitinib and pazopanib are the most recommended options for the first-line treatment of mRCC with clear-cell histology. Level of evidence: I. Grade of recommendation: A
- For patients with poor prognosis, temsirolimus is the only option supported by a phase III trial. Level of evidence: I. Grade of recommendation: A
- Sunitinib and pazopanib have also shown benefit in the treatment of poor-prognosis patients. Level of evidence: III. Grade of recommendation: B

Referenzen aus Leitlinien

First-line treatment in advanced disease:

- 31. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356(2):115–24.
- 32. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, 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):2103–11.
- 33. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Ou SS, 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):5422–8.
- 34. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010;28(6):1061–8.
- 35. 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;369:722–31.
- 36. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007;356(22):2271–81.

Leitlinienprogramm Onkologie, 2017[11].

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, Deutsche Krebsgesellschaft, Deutsche Krebshilfe.

Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms; S3-Leitlinie, Langversion 1.2.

Leitlinienorganisation/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

Grundlage der Leitlinie

- 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.

LoE: Verwendung nach Scottish Intercollegiate Guidelines Network (SIGN)

Recherche/Suchzeitraum:

- Initial bis 01/2013
- erste Aktualisierungsrecherche: 01/2014
- Aktualisierungsrecherchen für das Amendment 2016: 01/07/2016
- 3 Konsensuskonferenzen, finale schriftliche Abstimmung, DELPHI-Prozess

LoE

- Verwendung nach Scottish Intercollegiate Guidelines Network (SIGN)

Tabelle 3: Schema der Evidenzgraduierung nach SIGN

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

GoR

Tabelle 4: Schema der Empfehlungsgraduierung

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

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.

Sonstige methodische Hinweise

- 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/Referenzen aus Leitlinien:

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/Referenzen aus Leitlinien:

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/Referenzen aus Leitlinien:

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

7.4.	Evidenzbasierte Empfehlung	2015
Empfehlungsgrad A	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.	
Level of Evidence 1++	Literatur: [285, 287, 302]	
	Konsens	

7.5.	Evidenzbasierte Empfehlung	2015
Empfehlungsgrad A	Bei Patienten mit fortgeschrittenem und/oder metastasiertem klarzelligen Nierenzellkarzinom und ungünstigem Risikoprofil soll in der Erstlinientherapie Temsirolimus verwendet werden.	
Level of Evidence 1+	Literatur: [286]	
	Konsens	

Evidenzbasis/Referenzen aus Leitlinien:

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
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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
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Tab. 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

Kombinationstherapie des klarzelligen Nierenzellkarzinoms

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

Evidenzbasis/Referenzen aus Leitlinien:

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: 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

Ljungberg B et al., 2017 [12].

European Association of Urology (EAU)

Guidelines on renal cell carcinoma.

Fragestellung

The European Association of Urology (EAU) Renal Cell Cancer (RCC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of RCC.

Methodik

Grundlage der Leitlinie

The EAU RCC Guidelines were first published in 2000. This 2017 RCC Guidelines document presents a limited update of the 2016 publication.

Summary of changes: All chapters of the 2017 RCC Guidelines have been updated, based on the 2016 version of the guideline. References have been added throughout the document.

Recherche/Suchzeitraum:

- Suchzeitraum: The search was restricted to articles published between July 30th 2015 and June 30th 2016.
- The search was limited to studies representing high levels of evidence only (i.e. systematic reviews (SRs) with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies only) published in the English language.

LoE/GoR

- References used in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification

system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence.

Empfehlungen

Systemic therapy for advanced/metastatic RCC

Summary of evidence and recommendation for systemic therapy for advanced/metastatic renal cell cancer:

- In metastatic RCC, 5-FU combined with immunotherapy has equivalent efficacy to INF-α. [LE: 1b]
- In metastatic RCC, chemotherapy is otherwise not effective with the exception of gemcitabine and doxorubicine in sarcomatoid and rapidly progressive disease. [LE: 3]

Recommendations

- Do not offer chemotherapy as first-line therapy in patients with metastatic clear-cell renal cell cancer (RCC). [Grade: strong; ↓↓]
- Consider offering a combination of gemcitabine and doxorubicin to patients with sarcomatoid or rapidly progressive RCC. [Grade: weak; ↑]

Summary of evidence and recommendations for systemic therapy in metastatic renal cell cancer

- First line pazopanib is not inferior to sunitinib in clear-cell mRCC patients. [LE: 1b]
- Cabozantinib is superior to everolimus in terms of PFS and OS in patients failing one or more lines of VEGF-targeted therapy. [LE: 1b]
- Everolimus prolongs PFS in patients who have previously failed or are intolerant of VEGF-targeted therapy when compared to placebo. [LE: 1b]
- No combination has proven to be better than single-agent therapy, with the exception of the combination of lenvatinib plus everolimus. [LE: 1a]

Recommendations

- Offer sunitinib or pazopanib as first-line therapy for metastatic clear-cell renal cell cancer (ccRCC). [Grade: strong; ↑↑]
- Consider offering bevacizumab + Interferon (IFN)-α as first-line therapy for metastatic RCC in favourable-risk and intermediate-risk ccRCC. [Grade: weak; ↑]
- Consider offering temsirolimus as first-line treatment in poor-risk RCC patients. [Grade: weak; ↑]
- Offer cabozantinib for ccRCC after one or two lines of vascular endothelial growth factor (VEGF)-targeted therapy in metastatic RCC. [Grade: strong; ↑↑]
- Sunitinib can be offered as first-line therapy for non-clear cell mRCC. [Grade: weak; ↑]

Immunotherapy

Summary of evidence and recommendations for immunotherapy in mRCC

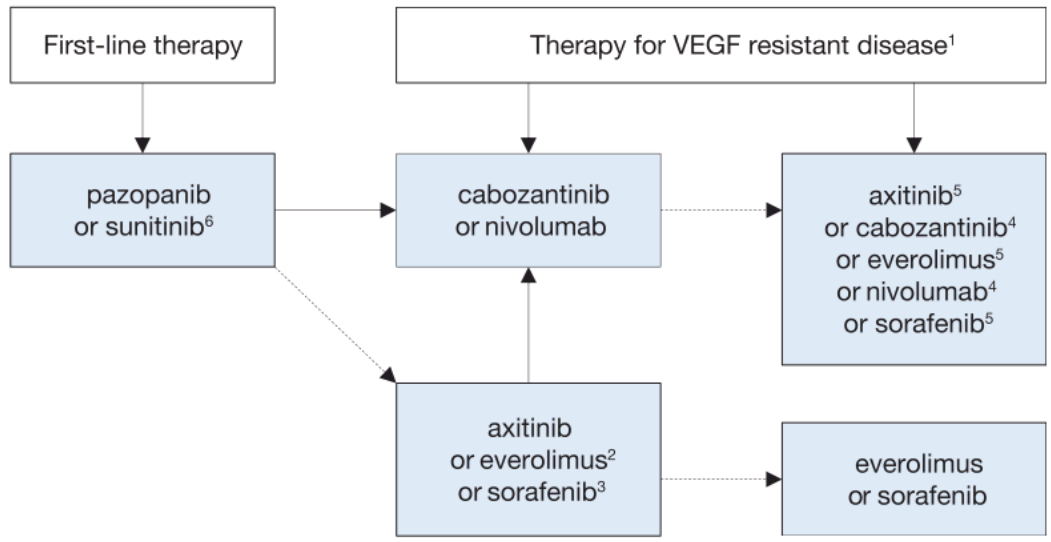
- Interferon-α monotherapy is inferior to VEG-targeted therapy or mTOR inhibition in mRCC. [LE: 1b]
- Interleukin-2 monotherapy may have an effect in selected cases (good PS, ccRCC, lung metastases only). [LE: 2]
- IL-2 has more side-effects than IFN-α. [LE: 2]
- High dose (HD)-IL-2 is associated with 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. [LE: 1b]
- Bevacizumab plus IFN-α is more effective than IFN-α treatment-naïve, low-risk and intermediate-risk ccRCC. [LE: 1b]
- Vaccination therapy with tumour antigen 5T4 showed no survival benefit over first-line standard therapy. [LE: 1b]
- Cytokine combinations, with or without additional chemotherapy, do not improve OS compared with monotherapy. [LE: 1b]
- Nivolumab leads to superior OS compared to everolimus in patients failing one or two lines of VEGF-targeted therapy. [LE: 1b]

Recommendations

- Offer nivolumab after one or two lines of vascular endothelial growth factor-targeted therapy in metastatic RCC. [Grade: strong; ↑↑]
- Do not offer monotherapy with interferon-α or high-dose bolus interleukin-2 as first-line therapy in metastatic RCC. [Grade: weak; ↓]

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

Figure 7.1: Recommendations for patients with metastatic ccRCC who have failed one or more lines of VEGF targeted therapy



[1] Switch to therapies not given previously.
[2] Nivolumab and cabozantinib have not been given after everolimus and therefore cannot be recommended above other agents.
[3] Sorafenib has an inferior progression-free survival to axitinib.
[4] These drugs have shown a survival advantage in VEGF-resistant disease but not in this specific setting.
[5] These drugs were given after progression in the pivotal cabozantinib or nivolumab trials [64, 172].
[6] Sunitinib and pazopanib can be recommended in all MSKCC risk groups. Bevacizumab/interferon (favourable- and intermediate-risk disease) and temsirolimus (poor-risk disease) have not been widely used as first-line therapy in the pivotal VEGF-resistant trials and therefore recommendations are not possible.

Hotte S et al., 2017 [8].

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 cancer: updated guideline 2017

Fragestellung

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

Grundlage der Leitlinie

- Update der Version von 2009
- Suche nach und Anpassung von existierenden Leitlinien
- Systematische Literaturrecherche
- interner und externer Review-Prozess

Recherche/Suchzeitraum:

- Suchzeitraum (Update): 2008 – 04/2016

LoE/GoR:

- PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation.
- 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: Type of Recommendation and Level of Obligation
- Questions: At what level of obligation should the reader feel the recommended action should be followed?
- Judgements/Options: Must (strong recommendation), Should, May (weak recommendation or consensus statement)

Sonstige methodische Hinweise

- Empfehlungen mit Evidenz verknüpft
- 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.

Qualifying Statements

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.

Interpretation of Evidence for Recommendation

Sunitinib and pazopanib appear equally effective. Oncologists should discuss and assess the different toxicity profiles of the two drugs with their patients.

Key Evidence

[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.
[6)] Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Ou S-S, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. Journal of Clinical Oncology. 2008;26(33):5422-8.
[7)] Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Archer L, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. Journal of Clinical Oncology. 2010;28(13):2137-43.

- 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.
[9)] Motzer RJ, Barrios CH, Kim TM, Falcon S, Cosgriff T, Harker WG, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. Journal of Clinical Oncology. 2014;32(25):2765-72.
[10)] Tannir NM, Jonasch E, Altinmakas E, Ng CS, Qiao W, Tamboli P, et al. Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (The ESPN Trial): A multicenter randomized phase 2 trial. Journal of Clinical Oncology. 2014;1).
[11)] .Armstrong AJ, Halabi S, Eisen T, Broderick S, Stadler WM, Jones RJ, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. The Lancet Oncology. 2016;17(3):378-88.

Benahmed N et al, 2015 [1].

Belgian Health Care Knowledge Centre (KCE)

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

Leitlinienorganisation/Fragestellung

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

Recherche/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]

Evidenzbasis

Sorafenib

113. Motzer RH, TE , Tomczak P, Michaelson M, Bukowski R, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell cancer. N Engl J Med. 2007;356:115-24.
129. Escudier B, Szczylik C, Hutson TE, Demkow T, Staehler M, Rolland F, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon alfa-2a in patients with metastatic renal cell carcinoma J. Clin. Oncol. 2009;27(13):1280-9.

130. Cella D, Li JZ, Cappelleri JC, Bushmakin A, Charbonneau C, Kim ST, et al. Quality of Life in Patients With Metastatic Renal Cell Carcinoma Treated With Sunitinib or Interferon Alfa: Results From a Phase III Randomized Trial. Journal of clinical oncology. 2008;26(22):3763-9.
131. Castellano D, del Muro XG, Perez-Gracia JL, Gonzalez-Larriba JL, Abrio MV, Ruiz MA, et al. Patient-reported outcomes in a phase III, randomized study of sunitinib versus interferon-{alpha} as first-line systemic therapy for patients with metastatic renal cell carcinoma in a European population. Ann Oncol. 2009;20(11):1803-12.
132. Cella D, Michaelson MD, Bushmakin AG, Cappelleri JC, Charbonneau C, Kim ST, et al. Health-related quality of life in patients with metastatic renal cell carcinoma treated with sunitinib vs interferon-alpha in a phase III trial: final results and geographical analysis. British journal of cancer. 2010;102(4):658-64.
133. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. Journal of clinical oncology. 2009;27(22):3584-90.
134. Patil S, Figlin RA, Hutson TE, Michaelson MD, Negrier S, Kim ST, et al. Q-TWiST analysis to estimate overall benefit for patients with metastatic renal cell carcinoma treated in a phase III trial of sunitinib vs interferon-? British journal of cancer. 2012;106(10):1587-90.
Cella D, Davis MP, Negrier S, Figlin RA, Michaelson MD, Bushmakin AG, et al. Characterizing fatigue associated with sunitinib and its impact on health-related quality of life in patients with metastatic renal cell carcinoma. Cancer. 2014.
147. Hutson TE, Lesovoy V, Al-Shukri S, Stus VP, Lipatov ON, Bair AH, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: A randomised open-label phase 3 trial. Lancet Oncol. 2013;14(13):1287-94.
148. Procopio G, Verzoni E, Bracarda S, Ricci S, Sacco C, Ridolfi L, et al. Sorafenib with interleukin-2 vs sorafenib alone in metastatic renal cell carcinoma: the ROSORC trial. British journal of cancer.
2011;104(8):1256-61.
149. Procopio G, Verzoni E, Bracarda S, Ricci S, Sacco C, Ridolfi L, et al. Overall survival for sorafenib plus interleukin-2 compared with sorafenib alone in metastatic renal cell carcinoma (mRCC): Final results of the ROSORC trial. Annals of oncology. 2013;24(12):2967-71.
150. Jonasch E, Corn P, Pagliaro LC, Warneke CL, Johnson MM, Tamboli P, et al. Upfront, randomized, phase 2 trial of sorafenib versus sorafenib and low dose interferon alfa in patients with advanced renal cell carcinoma. Cancer 2010;116:57–65.

Temsirolimus
120. Dutcher JP, de Souza P, McDermott D, Figlin RA, Berkenblit A, Thiele A, et al. Effect of temsirolimus versus interferon-on outcome of patients with advanced renal cell carcinoma of different histologies. Med Oncol. 2009;26(2):202-9.
136. 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 Engl. J. Med. 2007;356(22):2271-81.
137. Yang S, De Souza P, Alemao E, Purvis J. Quality of life in patients with advanced renal cell carcinoma treated with temsirolimus or interferon-(alpha). Br. J. Cancer. 2010;102(10):1456-60.
138. Zbrozek AS, Hudes G, Levy D, Strahs A, Berkenblit A, DeMarinis R, et al. Q-TWiST analysis of patients receiving temsirolimus or interferon alpha for treatment of advanced renal cell carcinoma. PharmacoEconomics. 2010;28(7):577-84.
139. Alemao E, Rajagopalan S, Yang S, Curiel RE, Purvis J, Al MJ. Inverse probability weighting to control for censoring in a post hoc analysis of quality-adjusted survival data from a clinical trial of temsirolimus for renal cell carcinoma. Journal of medical economics. 2011;14(2):245-52.
140. Maroto JP, Hudes G, Dutcher JP, Logan TF, White CS, Krygowski M, et al. Drug-related pneumonitis in patients with advanced renal cell carcinoma treated with temsirolimus. J Clin Oncol.
2011;29(13):1750-6.

Bevacizumab
115. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szcylik C, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet. 2007;370:2103-11.
141. Melichar B, Koralewski P, Ravaud A, Pluzanska A, Bracarda S, Szczylik C, et al. First-line bevacizumab combined with reduced dose interferon-α2a is active in patients with metastatic renal cell carcinoma. Annals of Oncology 2008;19:1470–6.
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145. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, S.S. O, 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):5422-8.
146. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Archer L, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol. 2010;28(13):2137-43.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 2 of 12, February 2019) am 20.12.2019

#	Suchfrage
1	[mh "Carcinoma, Renal Cell"]
2	((renal and cell) or kidney* or nephroid* or hypernephroid* or grawitz* or collecting duct):ti,ab,kw
3	(cancer* or tum*r* or carcinoma* or neoplas* or adenocarcinoma* or sarcoma* or lesion* 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 2014 to 2019

Systematic Reviews in Medline (PubMed) am 19.02.2019

#	Suchfrage
1	((((("carcinoma, renal cell/drug therapy"[mh] OR "carcinoma, renal cell/radiotherapy"[mh] OR "carcinoma, renal cell/therapy"[mh]))))
2	(renal[tiab] AND cell[tiab]) OR kidney*[tiab] OR nephroid*[tiab] OR hypernephroid*[tiab] OR grawitz*[tiab] OR collecting duct[tiab]
3	(((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]
4	hypernephroma*[tiab] OR rcc[tiab]
5	(#2 AND #3) OR #4
6	(#5) AND (treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab])
7	#1 OR #6
8	(#7) AND ((Meta-Analysis[ptyp] OR ((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND systematic review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (systematic review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab]

	OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))
9	((#8) AND ("2014/02/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 20.12.2019

#	**Suchfrage**
1	((((("carcinoma, renal cell/drug therapy"[mh] OR "carcinoma, renal cell/radiotherapy"[mh] OR "carcinoma, renal cell/therapy"[mh]))))
2	(renal[tiab] AND cell[tiab]) OR kidney*[tiab] OR nephroid*[tiab] OR hypernephroid*[tiab] OR grawitz*[tiab] OR collecting duct[tiab]
3	(((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]
4	hypernephroma*[tiab] OR rcc[tiab]
5	(#2 AND #3) OR #4
6	(#5) AND (treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab])
7	#1 OR #6
8	(#7) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
9	(((#8) AND ("2014/02/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))

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