Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-265-z Pembrolizumab + Axitinib

Stand: Dezember 2018

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

Pembrolizumab in Kombination mit Axitinib
zur Erstlinienbehandlung des fortgeschrittenen Nierenzellkarzinoms

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 zulassungsüberschreiten-den 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:	
Pembrolizumab L01XC18 KEYTRUDA®	KEYTRUDA ist in Kombination mit Axitinib zur Erstlinienbehandlung des fortgeschrittenen Nierenzellkarzinoms (RCC) bei Erwachsenen angezeigt (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.
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) − bei Erwachsenen nach vorangegangener zielgerichteter Therapie gegen VEGF (vaskulärer endothelialer Wachstumsfaktor).
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.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Sunitinib L01XE04 Sutent®	<u>Metastasierte Nierenzellkarzinome (mRCC)</u> SUTENT wird bei Erwachsenen zur Behandlung fortgeschrittener/ metastasierter Nierenzellkarzinome (mRCC) eingesetzt.
Tivozanib L01XE34 Fotvida®	Fotivda dient als Erstlinientherapie bei erwachsenen Patienten mit fortgeschrittenem Nierenzellkarzinom (NZK) sowie als Therapie bei erwachsenen Patienten, die noch nicht mit VEGFR- und mTOR-Signalweginhibitoren behandelt wurden und bei denen es nach einer vorherigen Cytokin-Therapie für fortgeschrittene NZK zur Krankheitsprogression kam.
mTOR-Inhibitoren	
Temsirolimus L01XE09 Torisel®	<u>Nierenzellkarzinom</u> Torisel ist angezeigt zur *first-line*-Behandlung des fortgeschrittenen Nierenzellkarzinoms (*renal cell carcinoma*, RCC) bei erwachsenen Patienten, die mindestens 3 von 6 prognostischen Risikofaktoren aufweisen (siehe Abschnitt 5.1).
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: 2018-B-265-z

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	28. November 2018

Gemeinsamer Bundesausschuss

Inhaltsverzeichnis

Gemeinsamer Bundesausschuss

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

„Behandlung des fortgeschrittenen Nierenzellkarzinoms bei Erwachsenen“

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Nierenzellkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 23.04.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1272 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 27 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

G-BA, 2018 [10].

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 [20].

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 [11].

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 (Neubewertung nach Fristablauf) vom 5. April 2018

Siehe auch IQWiG, 2017 [16,17]

Anwendungsgebiet (laut Zulassung vom 9. September 2016):

CABOMETYX™ ist indiziert (renal cell für die Behandlung des fortgeschrittenen Nierenzellkarzinoms carcinoma, RCC) bei Erwachsenen nach vorangegangener zielgerichteter Therapie gegen VEGF (vaskulärer endothelialer Wachstumsfaktor)

Zweckmäßige Vergleichstherapie:

Nivolumab oder Everolimus

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Everolimus:

Hinweis auf einen geringen Zusatznutzen.

G-BA, 2017 [7].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Axitinib (Ablauf der Befristung) vom 21. September 2017

Siehe auch IQWiG, 2017 [15].

Anwendungsgebiet (laut Zulassung vom 3. September 2012):

Inlyta ist angezeigt zur Behandlung des fortgeschrittenen Nierenzellkarzinoms (renal cell cancer, RCC) bei erwachsenen Patienten nach Versagen von vorangegangener Therapie mit Sunitinib oder einem Zytokin.

a) Nach vorangegangener Therapie mit Sunitinib:

Zweckmäßige Vergleichstherapie:

Nivolumab oder Everolimus

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Nivolumab

Ein Zusatznutzen ist nicht belegt.

b) Nach vorangegangener Therapie mit einem Zytokin:

Zweckmäßige Vergleichstherapie:

Sorafenib

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Sorafenib:

Anhaltspunkt für einen geringen Zusatznutzen.

G-BA, 2017 [8].

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 – Lenvatinib (neues Anwendungsgebiet: fortgeschrittenes Nierenzellkarzinom)

Siehe auch IQWiG, 2016 [18].

Zugelassenes Anwendungsgebiet (laut Zulassung vom 25. August 2016):

Kisplyx ist indiziert in Kombination mit Everolimus zur Behandlung von erwachsenen Patienten mit fortgeschrittenem Nierenzellkarzinom (renal cell carcinoma, RCC) nach einer vorhergehenden, gegen den vaskulären endothelialen Wachstumsfaktor (VEGF) gerichteten Behandlung.

Zweckmäßige Vergleichstherapie:

Nivolumab oder Everolimus

Fazit / Ausmaß des Zusatznutzens gegenüber Everolimus:

Anhaltspunkt für einen geringen Zusatznutzen.

G-BA, 2016 [9].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Nivolumab (neues Anwendungsgebiet).

Siehe auch IQWiG, 2016 [19]

Zugelassenes Anwendungsgebiet (laut Zulassung vom 04.04.2016):

Nierenzellkarzinom (RCC)

OPDIVO ist als Monotherapie bei Erwachsenen zur Behandlung des fortgeschrittenen Nierenzellkarzinoms nach Vortherapie indiziert.

1) Patienten nach antiangiogenetischer Vortherapie

Zweckmäßige Vergleichstherapie:

Everolimus

Fazit / Ausmaß des Zusatznutzens gegenüber Everolimus

Hinweis auf einen beträchtlichen Zusatznutzen.

2) Patienten nach Vortherapie mit Temsirolimus

Zweckmäßige Vergleichstherapie:

Sunitinib

Fazit / Ausmaß des Zusatznutzens gegenüber Sunitinib

Ein Zusatznutzen ist nicht belegt.

G-BA, 2009 [6].

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 [25].

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.

3.3 Systematische Reviews

Schmidt E et al, 2018 [24].

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 check-list

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.

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.

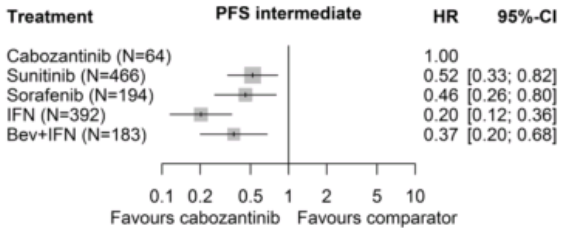

Fig. 2 PFS network meta-analysis forest plots — intermediate-risk group *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: Interferon; *PFS*: progression-free survival

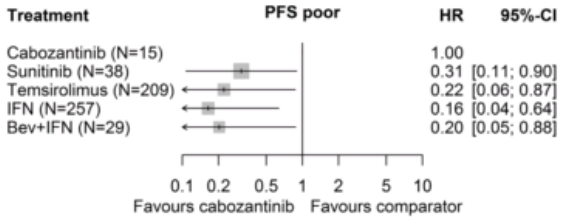

Fig. 3 PFS network meta-analysis forest plots — poor risk-group *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *PFS*: progression-free survival

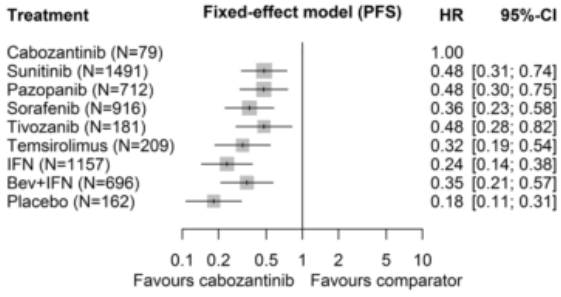

Fig. 4 PFS network meta-analysis forest plots — overall-risk group *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *PFS*: progression-free survival

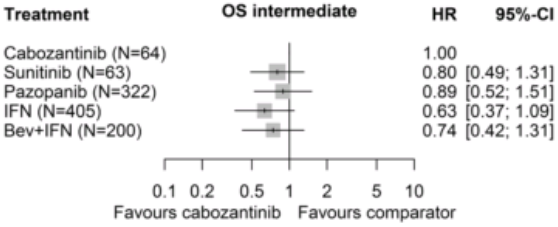

Fig. 5 OS network meta-analysis forest plots — intermediate-risk group. *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *OS*: overall survival

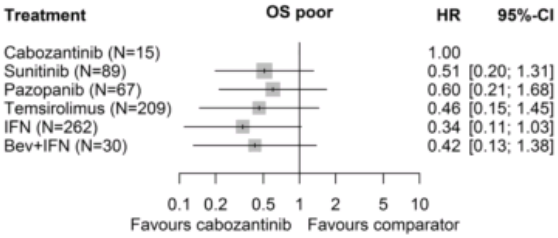

Fig. 6 OS network meta-analysis forest plots — poor-risk group. *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *OS*: overall survival

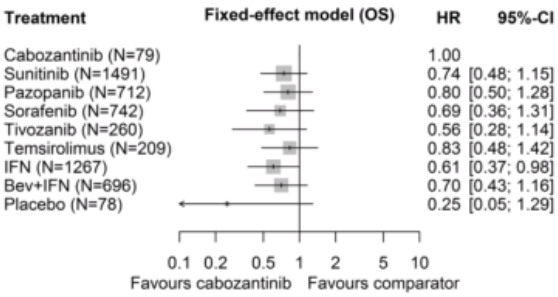

Fig. 7 OS network meta-analysis forest plots — overall-risk group. *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *OS*: overall survival

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.

Wei C et al, 2018 [27].

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 significant 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. 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.

Edwards SJ et al, 2018 [4].

Axitinib, cabozantinib, everolimus, nivolumab, sunitinib and best supportive care in previously treated renal cell carcinoma: a systematic review and economic evaluation.

Fragestellung

- evaluate the clinical effectiveness and cost-effectiveness of axitinib, best supportive care (BSC), cabozantinib, nivolumab, everolimus for treated amRCC in line with their respective marketing authorisations
- identify key areas for further primary and secondary research.

Methodik

Population:

- Patients with previously treated amRCC

Intervention:

For people who have received previous VEGF-targeted therapy:

- axitinib
- cabozantinib
- everolimus
- nivolumab
- sunitinib

Komparator:

- The interventions listed above compared with each other
- BSC

Endpunkte:

- Overall survival
- Progression-free survival
- Response rates
- Adverse events of treatment
- HRQoL

Recherche/Suchzeitraum:

- From inception to 01 and 07/2016

Qualitätsbewertung der Studien:

- Study quality was assessed according to recommendations by the CRD and the Cochrane Handbook for Systematic Reviews of Interventions.
- Study quality for the non-randomised studies was assessed using the Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Twelve studies (n = 4144) met the inclusion criteria: four RCTs (one double-blind RCT and three open-label RCTs) and eight non-RCTs (six retrospective cohort studies and two crossover RCTs in which only second-phase data were relevant).

Charakteristika der Population:

- Populations were predominantly male and white, and the mean age was generally between 60 and 70 years.
- When reported, most patients had stage 3 or 4 clear-cell renal cell carcinoma (RCC) and reasonably good baseline performance status.

Qualität der Studien:

- Siehe Anhang

Studienergebnisse:

- The primary PFS analysis, based on two RCTs (RECORD-1 and METEOR), included cabozantinib, everolimus and BSC and showed statistically significant benefits for cabozantinib and everolimus compared with BSC (HR 0.17, 95% CrI 0.12 to 0.24; and HR 0.33, 95% CrI 0.25 to 0.43, respectively), and for cabozantinib compared with everolimus (HR 0.51, 95% CrI 0.41 to 0.63).
- The primary OS analysis, based solely on RCT data, included cabozantinib, everolimus, nivolumab and BSC, and did not show statistically significant benefits for any treatment
- The primary ORR analysis, based on three RCTs including cabozantinib, everolimus, nivolumab and BSC, showed statistically significant benefits of all treatments compared with BSC.
- Cabozantinib and nivolumab resulted in statistically significant improvements in ORR compared with everolimus (OR 6.67, 95%CrI 3.28 to 12.78; and OR 6.18, 95%CrI 3.75 to

9.84, respectively). The difference between nivolumab and cabozantinib was not statistically significant for ORR compared with BSC.

- Treatments could not be compared using MTC for HRQoL as different measures and tools were used for assessments.

Anmerkung/Fazit der Autoren

The RCT evidence suggests that cabozantinib is likely to be the most effective for PFS and OS, closely followed by nivolumab. All treatments appear to delay disease progression and prolong survival compared with BSC, although the results are heterogeneous. The economic analysis shows that at list price everolimus could be recommended as the other drugs are much more expensive with insufficient incremental benefit. The applicability of these findings to the NHS is somewhat limited because existing confidential patient access schemes could not be used in the analysis. Future work using the discounted prices at which these drugs are provided to the NHS would better inform estimates of their relative cost-effectiveness.

Kommentare zum Review

- Limitations: Treatment comparisons were limited by the small number of RCTs. However, the key limitation of the analysis is the absence of the drug prices paid by the NHS, which was a limitation that could not be avoided owing to the confidentiality of discounts given to the NHS.
- Funding: The National Institute for Health Research Health Technology Assessment programme.

Rousseau B et al, 2016 [23].

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:

- Gemäß Cochrane risk of bias tool

Netzwerk-Metaanalyse

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

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 RCTs / 4282 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

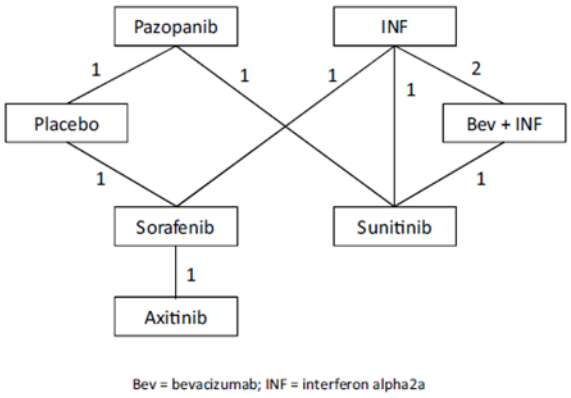

Fig. 3. Network of treatment comparisons established for the nine selected two-arm clinical trials. Lines between agents represent direct comparisons. The numbers represent the number of trial arms providing direct comparison between the angiogenic agents. Bev = bevacizumab; INF = interferon alpha2a.

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.

Anmerkung/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.

Wang L et al., 2015 [26].

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%

Anmerkung/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).

Iacovelli R et al, 2015 [14].

Inhibition of the VEGF/VEGFR pathway improves survival in advanced kidney cancer: a systematic review and meta-analysis.

Fragestellung

The effect of antiangiogenic therapies on overall survival in mRCC patients.

Methodik

Population:

- mRCC patients

Intervention:

- anti-VEGF/VEGFR agent

Komparator:

- non anti-VEGF/VEGFR agent: treatment with placebo or interferon (IFN)

Endpunkt:

- Overall survival (OS)

Recherche/Suchzeitraum:

- 01/2005 to 07/2013

Qualitätsbewertung der Studien:

- Jadad seven-item scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTs / 3469 Patienten

Charakteristika der Population:

- All studies enrolled patients with clear-cell mRCC

Qualität der Studien:

- In all trials, patients were randomly allocated, all were phase III studies, three were double-blind trials.

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

Studienergebnisse:

Wirksamkeit in Bezug auf den Endpunkt "Overall Survival"

Erstlinie

Subpopulation: treatment naïve patients

- Treatment with the anti-VEGF/VEGFR agents decreased the risk of death (HR=0.88; 95%CI, 0.79 – 0.97; *p*=0.010) compared to control (control arm: 1,149 patients: 1,071 received IFN-alph and 78 received placebo). 4 RCT, 2364 patients; keine signifikante Heterogenität (Chi^2=1.31, p=0.73, I^2=0%).
- No differences were found between the anti-VEGFR (TKIs) and the anti-VEGF agents (monoclonal antibody) in terms of the decrease in the risk of death (*p*=0.86).

Zweitlinie

keine Subgruppenanalyse durchgeführt

Anmerkung/Fazit der Autoren

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

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

Iacovelli R et al, 2014 [13].

Targeted therapies and complete responses in first line treatment of metastatic renal cell carcinoma. A meta-analysis of published trials.

Fragestellung

We performed a meta-analysis of published reports about antiangiogenic agents (AA) versus placebo or immunotherapy, focusing on the incidence rates and the relative risk of radiological complete response (CR) in mRCC.

Methodik

Population:

- mRCC patients with good or intermediate prognosis

Intervention:

- Antiangiogenic agents (AAs) (sunitinib, sorafenib, pazopanib, and bevacizumab) as first line of therapy

Komparator:

- non-AAs: INF oder Plazebo

Endpunkt:

complete response (CR)

- Tumor response evaluations were based on Response Evaluation Criteria in Solid Tumors (RECIST)
- Evaluated by investigator and/or independent imaging-review committee

Recherche/Suchzeitraum:

- 01/2000-09/2012

Qualitätsbewertung der Studien:

- Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCT / 2747 Patienten

Charakteristika der Population:

- /

Qualität der Studien:

- For each patient, all imaging scans were evaluated by an independent imaging-review committee (IRC) blinded to study treatment, except for the bevacizumab trials.[5,6] In the latter, only the investigator assessment was performed.
- Randomized treatment allocation sequences were generated in all trials.
- Jadad' score was 3 for three studies and 5 for two studies (Table 1)

Table 1
Main characteristics of the included study.

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

Studienergebnisse:

Wirksamkeit in Bezug auf den Endpunkt “Complete Response”

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

Subgroup analysis by “prognosis”

- No relationships were found between the rates of CRs and the rate of patients with good prognosis (p = 0.27).

Anmerkung/Fazit der Autoren

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

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

Amzal B et al, 2017 [2].

Cabozantinib versus everolimus, nivolumab, axitinib, sorafenib and best supportive care: A network meta-analysis of progression-free survival and overall survival in second line treatment of advanced renal cell carcinoma.

Fragestellung

The objective of the present study is to evaluate progression-free survival (PFS) and overall survival (OS) of cabozantinib compared to everolimus, nivolumab, axitinib, sorafenib, and best supportive care (BSC) in aRCC patients who progressed after previous VEGFR tyrosine-kinase inhibitor (TKI) treatment.

Methodik

Population:

- Patients with renal cell cancer (advanced / metastatic, previously treated)

Intervention:

- Cabozantinib

Komparator:

- Everolimus, axitinib, nivolumab, sorafenib, sunitinib, lenvatinib

Endpunkt:

- PFS
- OS
- Response rates
- Drug discontinuation
- Any other efficacy outcomes
- Safety outcomes
- Quality of life and other Patient-reported Outcomes
- Biomarkers for efficacy and safety

Recherche/Suchzeitraum:

- 06/2016

Qualitätsbewertung der Studien:

- Risk of bias was assessed with an adapted checklist for RCTs as proposed by the Centre for Reviews and Dissemination.

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 studies

Charakteristika der Population:

Anlage I

Qualität der Studien:

- The quality assessment of included trials showed that demographic and baseline characteristics were balanced between the treatment arms in all included studies.
- None of the studies reported unexpected dropouts between study groups.
- All 5 studies reported intent-to-treat (ITT) analysis and reported appropriate method to account for missing data.
- A potential risk of bias arises from investigators, participants and outcome assessors not being blind to treatment allocation in all studies. Effective blinding can ensure that the compared groups receive a similar amount of attention, ancillary treatment and diagnostic investigations.
- Blinding is not always possible, however, and three of the studies were not double blinded

Studienergebnisse:

- The log-normal fixed-effects model displayed the best fit of data for both PFS and OS, and showed that patients on cabozantinib had a higher probability of longer PFS and OS than patients exposed to comparators.
- The survival advantage of cabozantinib increased over time for OS.
- For PFS the survival advantage reached its maximum at the end of the first year's treatment and then decreased over time to zero.

Table 12. Subgroup results–availability of HR results by prognostic score.

End-point	Study	Comparator	Baseline	HR for poor prognosis [95% CI]	HR for intermediate prognosis [95% CI]	HR for favourable prognosis [95% CI]
OS	CheckMate025	Nivolumab	Everolimus	0.47 [0.30, 0.73]	0.76 [0.58, 0.99]	0.89 [0.59, 1.32]
OS	METEOR	Cabozantinib	Everolimus	0.65 [0.39, 1.07]	0.67 [0.48, 0.94]	0.66 [0.46, 0.96]
PFS	AXIS	Axitinib	Sorafenib	0.68 [0.49, 0.94]	0.80 [0.58, 1.10]	0.50 [0.33, 0.76]
PFS	RECORD-1	Everolimus	Placebo	0.44 [0.22, 0.85]	0.32 [0.22, 0.44]	0.31 [0.19, 0.50]
PFS	METEOR	Cabozantinib	Everolimus	0.70 [0.42, 1.16]	0.47 [0.35, 0.62]	0.51 [0.38, 0.69]

Table 13. Sources of OS (ITT), OS (cross-over adjusted), PFS IRC-, and PFS INV-assessed KM plots and hazard ratio results.

HR (95% confidence interval)	OS ITT	OS Cross-over adjusted	PFS Independent review committee (IRC)	PFS Investigator assessed (INV)
METEOR	0.66 (0.53–0.83) Patient level data (published in Fig 2 [14])	Not applicable	0.51 (0.41–0.62) Patient level data (published in Fig 4 [14])	Not applicable
RECORD-1	0.87 (0.65–1.15) Fig 6A [20]	0.60 (0.22–1.65) Fig 5	0.30 (0.22–0.40) Fig 2 [45]	Not applicable, IRC PFS available
CheckMate025	0.73 (0.57–0.93) Fig 1 [14]	Not applicable	Not available	0.88 (0.75–1.03) Fig 2B [14]
TARGET	0.88 (0.74–1.04) Fig1A [21]	Fig 1B [21]	0.44 (0.35–0.55) Fig 2C [47]	Not applicable, IRC PFS available
AXIS**	0.997 (0.78–1.27) Fig 2B [46]	Not applicable	0.741 (0.573–0.958) Fig 2C [22]	Not applicable, IRC PFS available

Key: OS, overall survival; ITT, intention to treat; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; KM, Kaplan-Meier; INV, investigator assessed; IRC, independent review committee assessed.

Note

** prior-sunitinib group results used in the analyses.

Anmerkung/Fazit der Autoren

With all five families of distributions, cabozantinib was superior to all its comparators with a higher probability of longer PFS and OSduring the analyzed 3 years, except with the Gompertz model, where nivolumab was preferred after 24 months.

Albiges L et al, 2015 [1].

EAU – European Association of Urology

A Systematic Review of Sequencing and Combinations of Systemic Therapy in Metastatic Renal Cancer.

Fragestellung

To systematically review relevant literature comparing the clinical effectiveness and harms of different sequencing and combinations of systemic targeted therapies for mRCC.

Methodik

Population:

- keine näheren Angaben

Intervention:

- combining or sequencing systemic targeted therapies

Komparator:

- aktive Substanz oder Placebo

Endpunkt:

- Primary endpoints: PFS, OS

Recherche/Suchzeitraum:

- the original EAU search was updated (covering the period from January 1, 2000, to September 30, 2013) methods protocol of the European Association of Urology (EAU) renal cell carcinoma 2013 guidelines was used as a basis for the search strategy
- Datenbanken: Medline, Medline In- Process, Embase, Cochrane Controlled Trials Register (Cochrane Library, Issue 8, 2013), and the Latin American and Caribbean Center on Health Sciences Information System. The search was complemented by additional sources including systematic reviews from the Cochrane Database of Systematic Reviews (Cochrane Library, Issue 8, 2013), recent conference proceedings of the American Society of Clinical Oncology and European Society of Medical Oncology, ongoing trials from clinicaltrials.gov and the World Health Organisation International Clinical Trials Registry

Qualitätsbewertung der Studien:

- Gemäß Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- n=24 RCTs (n= 9589 Patienten) für qualitative Betrachtung, n=4 für metaanalytische Auswertung

Charakteristika der Population:

- keine näheren Angaben

Qualität der Studien:

- RoB: There were generally low risks of bias across studies; however, clinical and methodological heterogeneity prevented pooling of data for most studies.

Studienergebnisse:

Cytokine pretreated patients

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

- Sunitinib, or other VEGF/VEGFR inhibiting therapies, have widely become the standard of care in the first-line setting.

post-VEGF/VEGFR inhibition setting

- studies investigating sequencing beyond the first-line setting had broad inclusion criteria and no stratification based on prognostic criteria!
- RCTs support the use of both mTOR inhibitors and VEGFR inhibition in the VEGFR TKI–resistant setting.
- AXIS trial is the only RCT comparing two TKIs (axitinib vs. sorafenib) following first-line VEGF inhibition: difference in PFS was significant in the favour of axitinib versus sorafenib, the gain in PFS was short, and no difference in OS was detected in the final analysis.
- INTORSECT study: direct comparison between different classes of agents (temsirolimus, ie, an mTOR inhibitor, vs sorafenib, ie, a VEGFR TKI) following progression on sunitinib, but it failed to define an optimal sequence because there was no statistical significant difference in PFS.
- RECORD-1 phase 3 RCT, designed to evaluate the mTOR inhibitor everolimus as second-line treatment versus placebo, have to be interpreted with caution because only 21% of the patients (53% received two previous treatments including one VEGFR inhibition plus cytokine) were purely second-line post sunitinib.

Kurzzusammenfassung der Studien siehe Table 1:

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

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

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

Anmerkung/Fazit der Autoren

Summarizing the available evidence, it can be concluded that both everolimus and axitinib are valid options after first-line VEGF/VEGFR inhibition failure. Sorafenib, in view of the recent OS results of the INTORSECT trial, might be considered as an alternative option. However, current PFS of second-line treatment is limited, with a median of 4–5 mo.mmentare zum Review

Kommentare zum Review
RCTs hatten häufig inhomogen vorbehandelte Studienpopulationen, siehe Tabelle 1 (oben); Aussagen sind somit einem hohen Verzerrungsrisiko unterworfen.

3.4 Leitlinien

Leitlinienprogramm Onkologie, 2017 [21].

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)

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

GoR

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

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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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

Zweitlinientherapie:

7.6.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **A**	Nach Versagen einer VEGF-basierten Therapie soll die Folgetherapie aus Nivolumab oder Cabozantinib bestehen. Eine spezifische Sequenz der Substanzen kann nicht empfohlen werden.	
Level of Evidence **1b**	Literatur: [320, 321]	
	Starker Konsens	

7.7.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **0**	Nach Versagen von Nivolumab oder Cabozantinib kann auf die jeweils andere Substanz gewechselt werden.	
Level of Evidence **4**	Literatur: [320, 321]	
	Starker Konsens	

7.8.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **0**	Nach Versagen eines VEGF Inhibitors kann die Kombination aus Lenvatinib + Everolimus zur Zweitlinienbehandlung eingesetzt werden.	
1-	Literatur: [322]	
	Starker Konsens	

7.9.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **0**	In der Zweitlinientherapie nach Sunitinib oder Zytokinen kann Axitinib verwendet werden.	
Level of Evidence **1+**	Literatur: [323]	
	Starker Konsens	

7.10.	Evidenzbasierte Empfehlung	2015
Empfehlungsgrad 0	In der Zweitlinientherapie nach Zytokinen können Sorafenib oder Pazopanib als Alternative zu Axitinib eingesetzt werden.	
Level of Evidence 1+	Literatur: [324, 325]	
	Konsens	

7.11.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad 0	Nach Versagen von mindestens einem VEGF-Inhibitor kann Everolimus eingesetzt werden.	
Level of Evidence 1+	Literatur: [326]	
	Starker Konsens	

7.12.	Evidenzbasierte Empfehlung	2015
Empfehlungsgrad 0	Nach Versagen eines mTOR-Inhibitors kann die Folgetherapie mittels eines Tyrosinkinaseinhibitors (TKI) erfolgen.	
Level of Evidence 2	Literatur: [327]	
	Konsens	

7.13.	Evidenzbasiertes Statement	2017
Level of Evidence 4	Patienten, die eine Therapie mit Nivolumab erhalten sollen engmaschig und bis zu 12 Monate nach Therapieende auf immunvermittellte Nebenwirkungen kontrolliert werden. Treten Immuntherapie-assoziierte Nebenwirkungen auf, sollen diese umgehend therapiert werden.	
	Literatur: [320, 321]	
	Starker Konsens	

Evidenzbasis/Referenzen aus Leitlinien:

- [320.] Motzer, R.J., et al., Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med, 2015. 373(19): p. 803-13. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/26406148
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- [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

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Tab. 12: Systemtherapieoptionen gemäß Vortherapie in der Zweitlinientherapie

Therapielinie	Vortherapie	Standard	Option
Zweitlinie	nach Zytokinen	Axitinib	Pazopanib Sorafenib
	nach VEGF-Versagen	Cabozatntinib Nivolumab	Axitinib (nach Sunitinib) Everolimus Lenvatinib+Everolimus
	nach Temsirolimus	Axitinib Cabozantinib Pazopanib Sorafenib Sunitinib	

Sequenztherapie des klarzelligen Nierenzellkarzinoms

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

Evidenzbasis/Referenzen aus Leitlinien:

327. Motzer, R.J., et al., Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: an open-label, randomised phase 3 trial. Lancet Oncol, 2014. 15(3): p. 286-96.
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349. Michel, M.S., et al., SWITCH: A randomized sequential open-label study to evaluate efficacy and safety of sorafenib (SO)/sunitinib (SU) versus SU/SO in the treatment of metastatic renal cell cancer (mRCC). J Clin Oncol (Meeting Abstracts), 2014. 32(4_suppl): p. 393-. PubMed: http://meeting.ascopubs.org/cgi/content/abstract/32/4_suppl/393

Kombinationstherapie des klarzelligen Nierenzellkarzinoms

- Eine Kombinationstherapie mit zwei zielgerichteten Therapien soll derzeit nur innerhalb von klinischen Studien durchgeführt 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

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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
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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

Gallardo E et al, 2018 [5].

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

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

Leitlinienorganisation/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

Second-line treatment in advanced disease

- Nivolumab and cabozantinib have shown increased OS in patients with advanced ccRCC previously treated with antiangiogenics, and are the recommended treatments for these patients. Level of evidence: I. Grade of recommendation: A
- Decisions to use either agent may be based on the expected toxicity and on contraindications for each drug, as randomized data is lacking. Level of evidence: IV. Grade of recommendation: D
- Lenvatinib in combination with everolimus has shown increased OS in patients with advanced ccRCC in a randomized phase II trial, and is another valid alternative for these patients. Level of evidence: II. Grade of recommendation: B
- Axitinib and everolimus have not shown increased OS after prior antiangiogenic therapy and should not be used before the previous agents. Nevertheless they may remain acceptable options following such agents, although they have not been tested in randomized trials in this setting. Level of evidence: II. Grade of recommendation: B

Referenzen aus Leitlinien

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- 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.
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- 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.
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Second-line treatment in advanced disease:

- 37. 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;373:1803–13.
- 38. Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373:1814–23.

- 39. Motzer RJ, Hutson TE, Glen H, Michaelson MD, Molina A, Eisen T, 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;16:1473–82.
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- 41. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356:125–34.
- 42. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008;372:449–56.

Ljungberg B et al, 2017 [22].

European Association of Urology (EAU)

Guidelines on renal cell carcinoma.

Leitlinienorganisation/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]

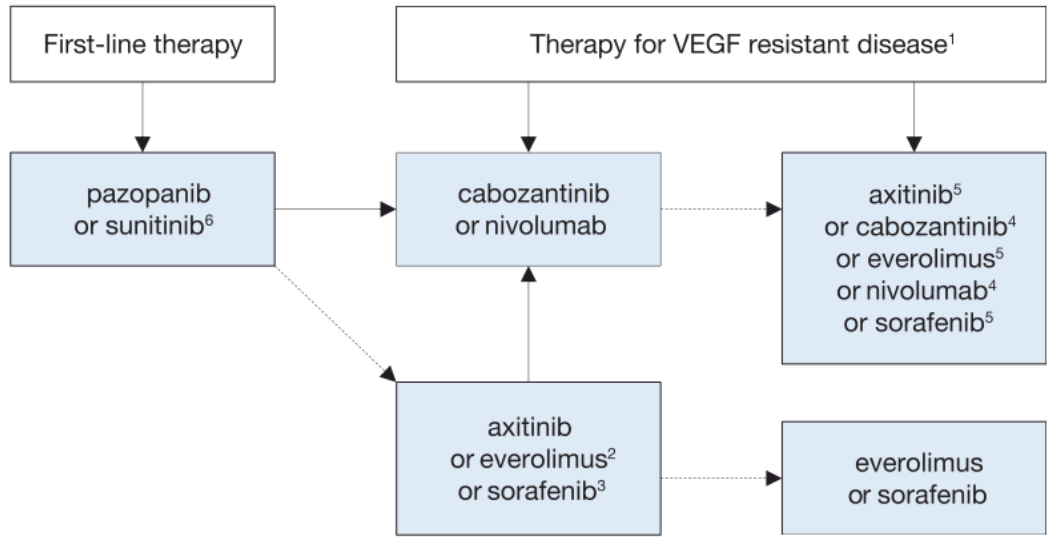
- Cytokine combinations, with or without additional chemotherapy, do not improve OS compared with monotherapy. [LE: 1b]
- Nivolumab leads to superior OS compared to everolimus in patients failing one or two lines of VEGF-targeted therapy. [LE: 1b]

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 [12]

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

Leitlinienorganisation/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 vernknüpft
- Studienqualität bewertet, aber nicht mit der Empfehlung verknüpft
- CoI offengelegt

Empfehlungen

Erstlinie

- Either of the vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGF TKIs) sunitinib or pazopanib is recommended for previously untreated patients with locally advanced or mRCC.

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.
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- Temsirolimus is a potential treatment option for first-line therapy for the subset of patients with poor-risk disease.

Qualifying Statements

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

Interpretation of Evidence for Recommendation

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

Key Evidence

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

Zweitlinie nach Zytokin-Therapie

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

Interpretation of Evidence for Recommendation

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

Key Evidence

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

Recommedations

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

Schlussfolgerungen aus dem Review

- Sorafenib improves PFS and CBR in comparison with placebo in low or intermediate risk mRCC patients. This advantage is also observed in sub-population such as elderly, prior cytokine treated patients. In addition, HRQoL is better rated by CC mRCC patients treated with sorafenib than by those treated with placebo whatever the patients' age (< 70 years vs ≥ 70 years).
- After cytokine treatment or in naïve patients, PFS, response rate are improved in CC mRCC patients treated with pazopanib in comparison to those treated with placebo. However, OS and HRQoL are not improved with this TKI.
- After IL-2, Bevacizumab (10 mg/kg or 3 mg/kg) improves PFS and OS in CC mRCC patients in comparison with placebo.
- After previous treatment with sunitinib, bevacizumab plus IFN-α, temsirolimus or cytokine, Axitinib improved PFS in comparison with Sorafenib in CC mRCC but no statistically significant difference in OS and QoL is observed.

Evidenzbasis

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 11.04.2018

#	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 tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or sarcoma* or malign*):ti,ab,kw
4	#2 and #3
5	(hypernephroma* or rcc):ti,ab,kw
6	#1 or #4 or #5
7	#6 Publication Year from 2013 to 2018

SR, HTAs in Medline (PubMed) am 12.04.2018

#	Suchfrage
1	((((("carcinoma, renal cell/drug therapy"[MeSH Terms] OR "carcinoma, renal cell/radiotherapy"[MeSH Terms] OR "carcinoma, renal cell/therapy"[MeSH Terms]))))
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]
4	hypernephroma*[tiab] OR rcc[tiab]
5	(#2 AND #3) OR #4
6	((((((((((treatment*[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 treating[tiab]) OR treated[tiab]) OR management[tiab]) OR drug*[tiab]
7	#5 AND #6
8	#1 OR #7
9	(#8) AND ((Meta-Analysis[ptyp] OR systematic[sb] 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]))))))
10	(#9) AND ("2013/04/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp])

Gemeinsamer Bundesausschuss

Leitlinien in Medline (PubMed) am 12.04.2018

#	Suchfrage
1	carcinoma, renal cell[MeSH Terms]
2	Kidney Neoplasms[Mesh:NoExp]
3	(renal[tiab] AND cell[tiab]) OR kidney*[tiab] OR nephroid*[tiab] OR hypernephroid*[tiab] OR grawitz*[tiab] OR collecting duct[tiab]
4	(((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]
5	#3 AND #4
6	hypernephroma*[tiab] OR rcc[tiab]
7	#1 OR #2 OR #5 OR #6
8	(Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[ti] OR recommendation*[ti]) NOT (letter[ptyp] OR comment[ptyp]))
9	#7 AND #8
10	(#9) AND ("2013/04/01"[PDAT] : "3000"[PDAT])

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Anhang

Edwards SJ et al, 2018 [4].

TABLE 5 Summary of Cochrane risk-of-bias assessment for RCTs

Criteria	Study			
	AXIS[43]	Checkmate-025[54]	METEOR[57]	RECORD-1[53]
General risk of bias				
Sources of bias related to study characteristics				
Random sequence allocation	✓	✓	✓	✓
Allocation concealment	✓	✓	✓	✓
Blinding: participant and personnel	✗	✗	✗	✓
Outcome specific				
PFS				
Blinding: outcome assessment	✓	✗	✓	✓
Incomplete outcome data	✓	✓	?	✓
Selective reporting	✓	✓	✓	✓
Other biases	?	?	N/A	?
Overall survival				
Blinding: outcome assessment	✓	✓	✓	✓
Incomplete outcome data	✓	?	?	✓
Selective reporting	✓	✓	✓	✓
Other biases	✓	✓	?	?

TABLE 5 Summary of Cochrane risk-of-bias assessment for RCTs (*continued*)

Criteria	Study			
	AXIS[43]	Checkmate-025[54]	METEOR[57]	RECORD-1[53]
Response rate				
Blinding: outcome assessment	✓	✗	✓	✓
Incomplete outcome data	?	✓	?	✓
Selective reporting	✓	✓	✓	?
Other biases	N/A	N/A	N/A	?
AEs				
Blinding: outcome assessment	✗	✗	✗	✓
Incomplete outcome data	✓	✓	✓	✓
Selective reporting	✓	✓	✓	✓
Other biases	N/A	?	N/A	N/A
HRQoL				
Blinding: outcome assessment	✗	✗	✗	✗
Incomplete outcome data	✓	✓	?	✓
Selective reporting	✓	✓	✓	✗
Other biases	N/A	N/A	N/A	N/A

✗, high risk; ✓, low risk; N/A, not applicable; ?, unclear risk.

TABLE 6 Summary of ROBINS-I risk-of-bias assessments in non-randomised studies

	Study									
	Calvani *et al.*, 2013[58]	ESPN[55]	Iacovelli *et al.*, 2015[59]	Paglino *et al.*, 2013[60]	Porta *et al.*, 2011[61]	SWITCH[56]	Vogelzang *et al.*, 2014[62]		Wong *et al.*, 2014[63]	
Outcome	PFS	PFS	OS	PFS	PFS	PFS	PFS	OS	PFS	OS
Confounding	✗	✗	✗	✗✗	✗✗	✗	~	~	~	~
Selection	✗	~	✗	✗	✗	~	✗	✗	✗	✗
Intervention classification	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Intervention deviations	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Missing data	~	✓	✓	NI	NI	✓	✓	✓	✗	✗
Outcome measures	✗	✓	✓	✗	✗	✗	✗	✓	✗	✓
Outcome reporting	~	✓	✓	~	~	~	✗	✓	✗	✓
Overall judgement	✗	✗	✗	✗✗	✗✗	✗	✗	✗	✗	✗

✗✗, critical risk; ✓, low risk; ~, moderate risk; NI, no information; ✗, serious risk.

Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-063 Pembrolizumab

Stand: Juni 2018

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

Pembrolizumab
[in Kombination mit Axitinib zur Behandlung des fortgeschrittenen Nierenzellkarzinoms]

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 5. April 2018 − Axitinib: Beschluss vom 21. September 2017 − Lenvatinib: Beschluss vom 16. März 2017 (Befristet bis zum 31. Dezember 2020) − Nivolumab: Beschluss vom 20. Oktober 2016 Negativer Beschluss über eine Änderung der 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 Beschluss des G-BA über Rücknahme eines Auftrags an die Expertengruppe Off-Label im Fachbereich Onkologie: Interferon-alpha und Interleukin-2-basierte Immunochemotherapien beim metastasierten Nierenzellkarzinom und in der adjuvanten Therapie – 15. Oktober 2009
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Pembrolizumab L01XC18 KEYTRUDA® Axitinib L01XE17 Inlyta®	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung:</u> KEYTRUDA ist als Kombinationstherapie mit Axitinib zur Behandlung des fortgeschrittenen Nierenzellkarzinoms bei Erwachsenen angezeigt.
Monoklonale Antikörper	
Bevacizumab L01XC07 Avastin®	Bevacizumab wird in Kombination mit Interferon alfa-2a zur *First-Line*-Behandlung von erwachsenen Patienten mit fortgeschrittenem und/oder metastasiertem Nierenzellkarzinom angewendet.
Tyrosin-Kinase-Inhibitoren	
Axitinib L01XE17 Inlyta®	Inlyta ist angezeigt zur Behandlung des fortgeschrittenen Nierenzellkarzinoms (*renal cell cancer*, RCC) bei erwachsenen Patienten nach Versagen von vorangegangener Therapie mit Sunitinib oder einem Zytokin.
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) − bei Erwachsenen nach vorangegangener zielgerichteter Therapie gegen VEGF (vaskulärer endothelialer Wachstumsfaktor).
Lenvatinib L01XE29 Kisplyx®	Kisplyx ist indiziert in Kombination mit Everolimus zur Behandlung von erwachsenen Patienten mit fortgeschrittenem Nierenzellkarzinom (*renal cell carcinoma, RCC)* nach einer vorhergehenden, gegen den vaskulären endothelialen Wachstumsfaktor (VEGF) gerichteten Behandlung.
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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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.
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.
Immun-Checkpoint-Inhibitoren	
Nivolumab L01XC17 Opdivo®	<u>Nierenzellkarzinom (RCC)</u> OPDIVO ist als Monotherapie bei Erwachsenen zur Behandlung des fortgeschrittenen Nierenzellkarzinoms nach Vortherapie indiziert.
mTOR-Inhibitoren	
Everolimus L01XE10 Afinitor®	<u>Nierenzellkarzinom</u> Afinitor ist zur Behandlung von Patienten mit fortgeschrittenem Nierenzellkarzinom indiziert, bei denen es während oder nach einer gegen VEGF gerichteten Therapie zu einer Krankheitsprogression kommt.
Temsirolimus L01XE09 Torisel®	<u>Nierenzellkarzinom</u> Torisel ist angezeigt zur *first-line*-Behandlung des fortgeschrittenen Nierenzellkarzinoms (*renal cell carcinoma*, RCC) bei erwachsenen Patienten, die mindestens 3 von 6 prognostischen Risikofaktoren aufweisen (siehe Abschnitt 5.1).
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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	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: 2018-B-063 (Pembrolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	22. Mai 2018

Gemeinsamer Bundesausschuss

Inhaltsverzeichnis

Gemeinsamer Bundesausschuss

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

„Behandlung des fortgeschrittenen Nierenzellkarzinoms bei Erwachsenen“

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Nierenzellkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 23.04.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1272 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 27 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

G-BA, 2018 [10].

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 [20].

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 [11].

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 (Neubewertung nach Fristablauf) vom 5. April 2018

Siehe auch IQWiG, 2017 [16,17]

Anwendungsgebiet (laut Zulassung vom 9. September 2016):

CABOMETYX™ ist indiziert (renal cell für die Behandlung des fortgeschrittenen Nierenzellkarzinoms carcinoma, RCC) bei Erwachsenen nach vorangegangener zielgerichteter

Therapie gegen VEGF (vaskulärer endothelialer Wachstumsfaktor)

Zweckmäßige Vergleichstherapie:

Nivolumab oder Everolimus

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Everolimus:

Hinweis auf einen geringen Zusatznutzen.

G-BA, 2017 [7].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Axitinib (Ablauf der Befristung) vom 21. September 2017

Siehe auch IQWiG, 2017 [15].

Anwendungsgebiet (laut Zulassung vom 3. September 2012):

Inlyta ist angezeigt zur Behandlung des fortgeschrittenen Nierenzellkarzinoms (renal cell cancer, RCC) bei erwachsenen Patienten nach Versagen von vorangegangener Therapie mit Sunitinib oder einem Zytokin.

a) Nach vorangegangener Therapie mit Sunitinib:

Zweckmäßige Vergleichstherapie:

Nivolumab oder Everolimus

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Nivolumab

Ein Zusatznutzen ist nicht belegt.

b) Nach vorangegangener Therapie mit einem Zytokin:

Zweckmäßige Vergleichstherapie:

Sorafenib

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Sorafenib:

Anhaltspunkt für einen geringen Zusatznutzen.

G-BA, 2017 [8].

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 – Lenvatinib (neues Anwendungsgebiet: fortgeschrittenes Nierenzellkarzinom)

Siehe auch IQWiG, 2016 [18].

Zugelassenes Anwendungsgebiet (laut Zulassung vom 25. August 2016):

Kisplyx ist indiziert in Kombination mit Everolimus zur Behandlung von erwachsenen Patienten mit fortgeschrittenem Nierenzellkarzinom (renal cell carcinoma, RCC) nach einer vorhergehenden, gegen den vaskulären endothelialen Wachstumsfaktor (VEGF) gerichteten Behandlung.

Zweckmäßige Vergleichstherapie

Nivolumab oder Everolimus

Fazit / Ausmaß des Zusatznutzens gegenüber Everolimus:

Anhaltspunkt für einen geringen Zusatznutzen.

G-BA, 2016 [9].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Nivolumab (neues Anwendungsgebiet).

Siehe auch IQWiG, 2016 [19]

Zugelassenes Anwendungsgebiet (laut Zulassung vom 04.04.2016):

Nierenzellkarzinom (RCC)

OPDIVO ist als Monotherapie bei Erwachsenen zur Behandlung des fortgeschrittenen Nierenzellkarzinoms nach Vortherapie indiziert.

1) Patienten nach antiangiogenetischer Vortherapie

Zweckmäßige Vergleichstherapie:

Everolimus

Fazit / Ausmaß des Zusatznutzens gegenüber Everolimus

Hinweis auf einen beträchtlichen Zusatznutzen.

2) Patienten nach Vortherapie mit Temsirolimus

Zweckmäßige Vergleichstherapie:

Sunitinib

Fazit / Ausmaß des Zusatznutzens gegenüber Sunitinib

Ein Zusatznutzen ist nicht belegt.

G-BA, 2009 [6].

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 [25].

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.

3.3 Systematische Reviews

Erstlinie / Unvorbehandelte Patienten

Schmidt E et al, 2018 [24].

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 check-

list

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.

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.

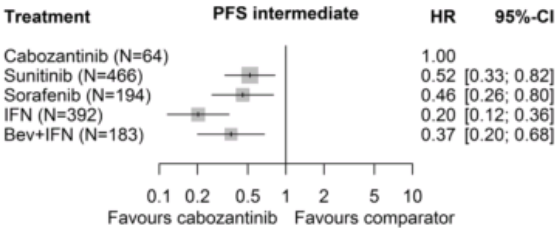

Fig. 2 PFS network meta-analysis forest plots — intermediate-risk group *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: Interferon; *PFS*: progression-free survival

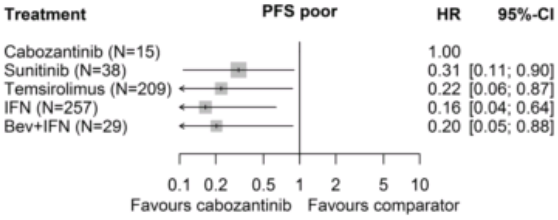

Fig. 3 PFS network meta-analysis forest plots — poor risk-group *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *PFS*: progression-free survival

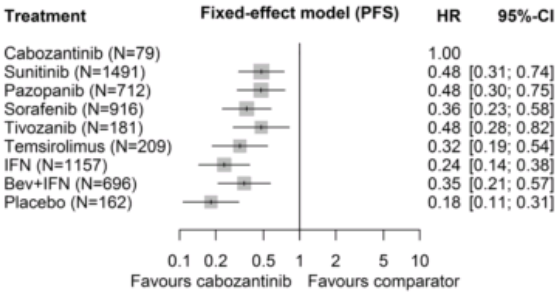

Fig. 4 PFS network meta-analysis forest plots — overall-risk group *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *PFS*: progression-free survival

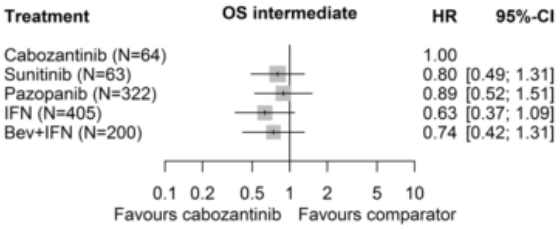

Fig. 5 OS network meta-analysis forest plots — intermediate-risk group. *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *OS*: overall survival

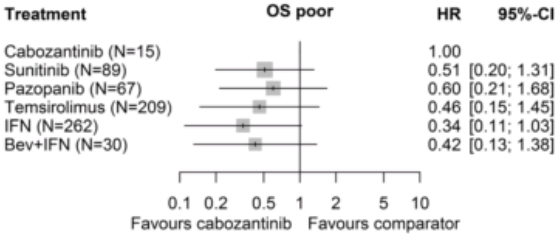

Fig. 6 OS network meta-analysis forest plots — poor-risk group. *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *OS*: overall survival

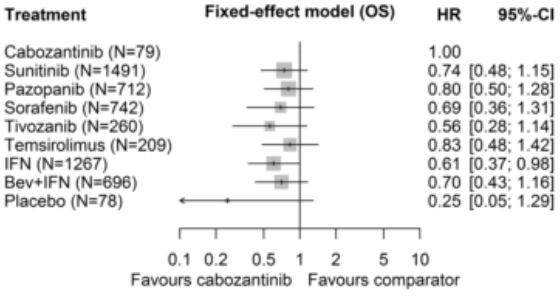

Fig. 7 OS network meta-analysis forest plots — overall-risk group. *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *OS*: overall survival

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.

Wei C et al, 2018 [27].

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 significant 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. 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.

Edwards SJ et al, 2018 [4].

Axitinib, cabozantinib, everolimus, nivolumab, sunitinib and best supportive care in previously treated renal cell carcinoma: a systematic review and economic evaluation.

Fragestellung

- evaluate the clinical effectiveness and cost-effectiveness of axitinib, best supportive care (BSC), cabozantinib, nivolumab, everolimus for treated amRCC in line with their respective marketing authorisations
- identify key areas for further primary and secondary research.

Methodik

Population:

- Patients with previously treated amRCC

Intervention:

For people who have received previous VEGF-targeted therapy:

- axitinib
- cabozantinib
- everolimus
- nivolumab
- sunitinib

Komparator:

- The interventions listed above compared with each other
- BSC

Endpunkte:

- Overall survival
- Progression-free survival
- Response rates
- Adverse events of treatment
- HRQoL

Recherche/Suchzeitraum:

- From inception to 01 and 07/2016

Qualitätsbewertung der Studien:

- Study quality was assessed according to recommendations by the CRD and the Cochrane Handbook for Systematic Reviews of Interventions.
- Study quality for the non-randomised studies was assessed using the Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Twelve studies (n = 4144) met the inclusion criteria: four RCTs (one double-blind RCT and three open-label RCTs) and eight non-RCTs (six retrospective cohort studies and two crossover RCTs in which only second-phase data were relevant).

Charakteristika der Population:

- Populations were predominantly male and white, and the mean age was generally between 60 and 70 years.
- When reported, most patients had stage 3 or 4 clear-cell renal cell carcinoma (RCC) and reasonably good baseline performance status.

Qualität der Studien:

- Siehe Anhang

Studienergebnisse:

- The primary PFS analysis, based on two RCTs (RECORD-1 and METEOR), included cabozantinib, everolimus and BSC and showed statistically significant benefits for cabozantinib and everolimus compared with BSC (HR 0.17, 95% CrI 0.12 to 0.24; and HR 0.33, 95% CrI 0.25 to 0.43, respectively), and for cabozantinib compared with everolimus (HR 0.51, 95% CrI 0.41 to 0.63).
- The primary OS analysis, based solely on RCT data, included cabozantinib, everolimus, nivolumab and BSC, and did not show statistically significant benefits for any treatment
- The primary ORR analysis, based on three RCTs including cabozantinib, everolimus, nivolumab and BSC, showed statistically significant benefits of all treatments compared with BSC.
- Cabozantinib and nivolumab resulted in statistically significant improvements in ORR compared with everolimus (OR 6.67, 95%CrI 3.28 to 12.78; and OR 6.18, 95%CrI 3.75

to 9.84, respectively). The difference between nivolumab and cabozantinib was not statistically significant for ORR compared with BSC.

- Treatments could not be compared using MTC for HRQoL as different measures and tools were used for assessments.

Anmerkung/Fazit der Autoren

The RCT evidence suggests that cabozantinib is likely to be the most effective for PFS and OS, closely followed by nivolumab. All treatments appear to delay disease progression and prolong survival compared with BSC, although the results are heterogeneous. The economic analysis shows that at list price everolimus could be recommended as the other drugs are much more expensive with insufficient incremental benefit. The applicability of these findings to the NHS is somewhat limited because existing confidential patient access schemes could not be used in the analysis. Future work using the discounted prices at which these drugs are provided to the NHS would better inform estimates of their relative cost-effectiveness.

Kommentare zum Review

- Limitations: Treatment comparisons were limited by the small number of RCTs. However, the key limitation of the analysis is the absence of the drug prices paid by the NHS, which was a limitation that could not be avoided owing to the confidentiality of discounts given to the NHS.
- Funding: The National Institute for Health Research Health Technology Assessment programme.

Rousseau B et al, 2016 [23].

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:

- Gemäß Cochrane risk of bias tool

Netzwerk-Metaanalyse

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

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 RCTs / 4282 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

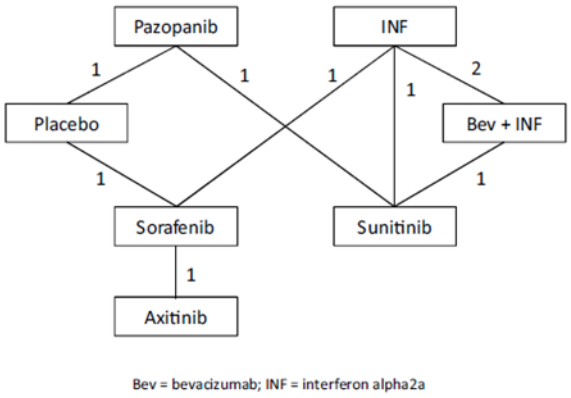

Fig. 3. Network of treatment comparisons established for the nine selected two-arm clinical trials. Lines between agents represent direct comparisons. The numbers represent the number of trial arms providing direct comparison between the angiogenic agents. Bev = bevacizumab; INF = interferon alpha2a.

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.

Anmerkung/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.

Wang L et al., 2015 [26].

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%

Anmerkung/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).

Iacovelli R et al, 2015 [14].

Inhibition of the VEGF/VEGFR pathway improves survival in advanced kidney cancer: a systematic review and meta-analysis.

Fragestellung

The effect of antiangiogenic therapies on overall survival in mRCC patients.

Methodik

Population:

- mRCC patients

Intervention:

- anti-VEGF/VEGFR agent

Komparator:

- non anti-VEGF/VEGFR agent: treatment with placebo or interferon (IFN)

Endpunkt:

- Overall survival (OS)

Recherche/Suchzeitraum:

- 01/2005 to 07/2013

Qualitätsbewertung der Studien:

- Jadad seven-item scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTs / 3469 Patienten

Charakteristika der Population:

- All studies enrolled patients with clear-cell mRCC

Qualität der Studien:

- In all trials, patients were randomly allocated, all were phase III studies, three were double-blind trials.

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

Studienergebnisse:

Wirksamkeit in Bezug auf den Endpunkt "Overall Survival"

Erstlinie

Subpopulation: treatment naïve patients

- Treatment with the anti-VEGF/VEGFR agents decreased the risk of death (HR=0.88; 95%CI, 0.79 – 0.97; *p*=0.010) compared to control (control arm: 1,149 patients: 1,071 received IFN-alph and 78 received placebo). 4 RCT, 2364 patients; keine signifikante Heterogenität (Chi^2=1.31, p=0.73, I^2=0%).
- No differences were found between the anti-VEGFR (TKIs) and the anti-VEGF agents (monoclonal antibody) in terms of the decrease in the risk of death (*p*=0.86).

Zweitlinie

keine Subgruppenanalyse durchgeführt

Anmerkung/Fazit der Autoren

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

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

Iacovelli R et al, 2014 [13].

Targeted therapies and complete responses in first line treatment of metastatic renal cell carcinoma. A meta-analysis of published trials.

Fragestellung

We performed a meta-analysis of published reports about antiangiogenic agents (AA) versus placebo or immunotherapy, focusing on the incidence rates and the relative risk of radiological complete response (CR) in mRCC.

Methodik

Population:

- mRCC patients with good or intermediate prognosis

Intervention:

- Antiangiogenic agents (AAs) (sunitinib, sorafenib, pazopanib, and bevacizumab) as first line of therapy

Komparator:

- non-AAs: INF oder Plazebo

Endpunkt:

complete response (CR)

- Tumor response evaluations were based on Response Evaluation Criteria in Solid Tumors (RECIST)
- Evaluated by investigator and/or independent imaging-review committee

Recherche/Suchzeitraum:

- 01/2000-09/2012

Qualitätsbewertung der Studien:

- Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCT / 2747 Patienten

Charakteristika der Population:

- /

Qualität der Studien:

- For each patient, all imaging scans were evaluated by an independent imaging-review committee (IRC) blinded to study treatment, except for the bevacizumab trials.[5,6] In the latter, only the investigator assessment was performed.
- Randomized treatment allocation sequences were generated in all trials.
- Jadad' score was 3 for three studies and 5 for two studies (Table 1)

Table 1
Main characteristics of the included study.

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

Studienergebnisse:

Wirksamkeit in Bezug auf den Endpunkt “Complete Response”

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

Subgroup analysis by “prognosis”

- No relationships were found between the rates of CRs and the rate of patients with good prognosis (p = 0.27).

Anmerkung/Fazit der Autoren

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

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

Zweitlinie / Vorbehandelte Patienten

Amzal B et al, 2017 [2].

Cabozantinib versus everolimus, nivolumab, axitinib, sorafenib and best supportive care: A network meta-analysis of progression-free survival and overall survival in second line treatment of advanced renal cell carcinoma.

Fragestellung

The objective of the present study is to evaluate progression-free survival (PFS) and overall survival (OS) of cabozantinib compared to everolimus, nivolumab, axitinib, sorafenib, and best

supportive care (BSC) in aRCC patients who progressed after previous VEGFR tyrosine-kinase inhibitor (TKI) treatment.

Methodik

Population:

- Patients with renal cell cancer (advanced / metastatic, previously treated)

Intervention:

- Cabozantinib

Komparator:

- Everolimus, axitinib, nivolumab, sorafenib, sunitinib, lenvatinib

Endpunkt:

- PFS
- OS
- Response rates
- Drug discontinuation
- Any other efficacy outcomes
- Safety outcomes
- Quality of life and other Patient-reported Outcomes
- Biomarkers for efficacy and safety

Recherche/Suchzeitraum:

- 06/2016

Qualitätsbewertung der Studien:

- Risk of bias was assessed with an adapted checklist for RCTs as proposed by the Centre for Reviews and Dissemination.

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 studies

Charakteristika der Population:

Anlage I

Qualität der Studien:

- The quality assessment of included trials showed that demographic and baseline characteristics were balanced between the treatment arms in all included studies.
- None of the studies reported unexpected dropouts between study groups.
- All 5 studies reported intent-to-treat (ITT) analysis and reported appropriate method to account for missing data.
- A potential risk of bias arises from investigators, participants and outcome assessors not being blind to treatment allocation in all studies. Effective blinding can ensure that the

compared groups receive a similar amount of attention, ancillary treatment and diagnostic investigations.

- Blinding is not always possible, however, and three of the studies were not double blinded

Studienergebnisse:

- The log-normal fixed-effects model displayed the best fit of data for both PFS and OS, and showed that patients on cabozantinib had a higher probability of longer PFS and OS than patients exposed to comparators.
- The survival advantage of cabozantinib increased over time for OS.
- For PFS the survival advantage reached its maximum at the end of the first year's treatment and then decreased over time to zero.

Table 12. Subgroup results–availability of HR results by prognostic score.

End-point	Study	Comparator	Baseline	HR for poor prognosis [95% CI]	HR for intermediate prognosis [95% CI]	HR for favourable prognosis [95% CI]
OS	CheckMate025	Nivolumab	Everolimus	0.47 [0.30, 0.73]	0.76 [0.58, 0.99]	0.89 [0.59, 1.32]
OS	METEOR	Cabozantinib	Everolimus	0.65 [0.39, 1.07]	0.67 [0.48, 0.94]	0.66 [0.46, 0.96]
PFS	AXIS	Axitinib	Sorafenib	0.68 [0.49, 0.94]	0.80 [0.58, 1.10]	0.50 [0.33, 0.76]
PFS	RECORD-1	Everolimus	Placebo	0.44 [0.22, 0.85]	0.32 [0.22, 0.44]	0.31 [0.19, 0.50]
PFS	METEOR	Cabozantinib	Everolimus	0.70 [0.42, 1.16]	0.47 [0.35, 0.62]	0.51 [0.38, 0.69]

Table 13. Sources of OS (ITT), OS (cross-over adjusted), PFS IRC-, and PFS INV-assessed KM plots and hazard ratio results.

HR (95% confidence interval)	OS ITT	OS Cross-over adjusted	PFS Independent review committee (IRC)	PFS Investigator assessed (INV)
METEOR	0.66 (0.53–0.83) Patient level data (published in Fig 2 [14])	Not applicable	0.51 (0.41–0.62) Patient level data (published in Fig 4 [14])	Not applicable
RECORD-1	0.87 (0.65–1.15) Fig 6A [20]	0.60 (0.22–1.65) Fig 5	0.30 (0.22–0.40) Fig 2 [45]	Not applicable, IRC PFS available
CheckMate025	0.73 (0.57–0.93) Fig 1 [14]	Not applicable	Not available	0.88 (0.75–1.03) Fig 2B [14]
TARGET	0.88 (0.74–1.04) Fig1A [21]	Fig 1B [21]	0.44 (0.35–0.55) Fig 2C [47]	Not applicable, IRC PFS available
AXIS**	0.997 (0.78–1.27) Fig 2B [46]	Not applicable	0.741 (0.573–0.958) Fig 2C [22]	Not applicable, IRC PFS available

Key: OS, overall survival; ITT, intention to treat; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; KM, Kaplan-Meier; INV, investigator assessed; IRC, independent review committee assessed.

Note

** prior-sunitinib group results used in the analyses.

Anmerkung/Fazit der Autoren

With all five families of distributions, cabozantinib was superior to all its comparators with a higher probability of longer PFS and OSduring the analyzed 3 years, except with the Gompertz model, where nivolumab was preferred after 24 months.

Fragestellung

To systematically review relevant literature comparing the clinical effectiveness and harms of different sequencing and combinations of systemic targeted therapies for mRCC.

Methodik

Population:

- keine näheren Angaben

Intervention:

- combining or sequencing systemic targeted therapies

Komparator:

- aktive Substanz oder Placebo

Endpunkt:

- Primary endpoints: PFS, OS

Recherche/Suchzeitraum:

- the original EAU search was updated (covering the period from January 1, 2000, to September 30, 2013) methods protocol of the European Association of Urology (EAU) renal cell carcinoma 2013 guidelines was used as a basis for the search strategy
- Datenbanken: Medline, Medline In- Process, Embase, Cochrane Controlled Trials Register (Cochrane Library, Issue 8, 2013), and the Latin American and Caribbean Center on Health Sciences Information System. The search was complemented by additional sources including systematic reviews from the Cochrane Database of Systematic Reviews (Cochrane Library, Issue 8, 2013), recent conference proceedings of the American Society of Clinical Oncology and European Society of Medical Oncology, ongoing trials from clinicaltrials.gov and the World Health Organisation International Clinical Trials Registry

Qualitätsbewertung der Studien:

- Gemäß Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- n=24 RCTs (n= 9589 Patienten) für qualitative Betrachtung, n=4 für metaanalytische Auswertung

Charakteristika der Population:

- keine näheren Angaben

Qualität der Studien:

- RoB: There were generally low risks of bias across studies; however, clinical and methodological heterogeneity prevented pooling of data for most studies.

Studienergebnisse:

Cytokine pretreated patients

- Sequencing targeted therapy as second-line treatment in cytokine pretreated patients has been assessed in randomized phase 2 (sunitinib) and large phase 3 RCTs for sorafenib, pazopanib, and axitinib. The average PFS in these reports was approximately 8 mo in cytokine-refractory patients.
- Sunitinib, or other VEGF/VEGFR inhibiting therapies, have widely become the standard of care in the first-line setting.

post-VEGF/VEGFR inhibition setting

- studies investigating sequencing beyond the first-line setting had broad inclusion criteria and no stratification based on prognostic criteria!
- RCTs support the use of both mTOR inhibitors and VEGFR inhibition in the VEGFR TKI–resistant setting.
- AXIS trial is the only RCT comparing two TKIs (axitinib vs. sorafenib) following first-line VEGF inhibition: difference in PFS was significant in the favour of axitinib versus sorafenib, the gain in PFS was short, and no difference in OS was detected in the final analysis.
- INTORSECT study: direct comparison between different classes of agents (temsirolimus, ie, an mTOR inhibitor, vs sorafenib, ie, a VEGFR TKI) following progression on sunitinib, but it failed to define an optimal sequence because there was no statistical significant difference in PFS.
- RECORD-1 phase 3 RCT, designed to evaluate the mTOR inhibitor everolimus as second-line treatment versus placebo, have to be interpreted with caution because only 21% of the patients (53% received two previous treatments including one VEGFR inhibition plus cytokine) were purely second-line post sunitinib.

Kurzzusammenfassung der Studien siehe Table 1:

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

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

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

Anmerkung/Fazit der Autoren

Summarizing the available evidence, it can be concluded that both everolimus and axitinib are valid options after first-line VEGF/VEGFR inhibition failure. Sorafenib, in view of the recent OS results of the INTORSECT trial, might be considered as an alternative option. However, current PFS of second-line treatment is limited, with a median of 4–5 mo.mmentare zum Review

Kommentare zum Review
RCTs hatten häufig inhomogen vorbehandelte Studienpopulationen, siehe Tabelle 1 (oben); Aussagen sind somit einem hohen Verzerrungsrisiko unterworfen.

3.4 Leitlinien

Leitlinienprogramm Onkologie, 2017 [21].

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)

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

GoR

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

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
- [287.] Escudier, B., et al., Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet, 2007. 370(9605): p. 2103-11. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18156031
- [302.] Motzer, R.J., et al., Pazopanib versus sunitinib in metastatic renal-cell carcinoma. The New England journal of medicine, 2013. 369(8): p. 722-731. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/23964934
- [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.

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

Zweitlinientherapie:

7.6.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **A**	Nach Versagen einer VEGF-basierten Therapie soll die Folgetherapie aus Nivolumab oder Cabozantinib bestehen. Eine spezifische Sequenz der Substanzen kann nicht empfohlen werden.	
Level of Evidence **1b**	Literatur: [320, 321]	
	Starker Konsens	

7.7.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **0**	Nach Versagen von Nivolumab oder Cabozantinib kann auf die jeweils andere Substanz gewechselt werden.	
Level of Evidence **4**	Literatur: [320, 321]	
	Starker Konsens	

7.8.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **0**	Nach Versagen eines VEGF Inhibitors kann die Kombination aus Lenvatinib + Everolimus zur Zweitlinienbehandlung eingesetzt werden.	
1-	Literatur: [322]	
	Starker Konsens	

7.9.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **0**	In der Zweitlinientherapie nach Sunitinib oder Zytokinen kann Axitinib verwendet werden.	
Level of Evidence **1+**	Literatur: [323]	
	Starker Konsens	

7.10.	Evidenzbasierte Empfehlung	2015
Empfehlungsgrad 0	In der Zweitlinientherapie nach Zytokinen können Sorafenib oder Pazopanib als Alternative zu Axitinib eingesetzt werden.	
Level of Evidence 1+	Literatur: [324, 325]	
	Konsens	

7.11.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad 0	Nach Versagen von mindestens einem VEGF-Inhibitor kann Everolimus eingesetzt werden.	
Level of Evidence 1+	Literatur: [326]	
	Starker Konsens	

7.12.	Evidenzbasierte Empfehlung	2015
Empfehlungsgrad 0	Nach Versagen eines mTOR-Inhibitors kann die Folgetherapie mittels eines Tyrosinkinaseinhibitors (TKI) erfolgen.	
Level of Evidence 2	Literatur: [327]	
	Konsens	

7.13.	Evidenzbasiertes Statement	2017
Level of Evidence 4	Patienten, die eine Therapie mit Nivolumab erhalten sollen engmaschig und bis zu 12 Monate nach Therapieende auf immunvermittellte Nebenwirkungen kontrolliert werden. Treten Immuntherapie-assoziierte Nebenwirkungen auf, sollen diese umgehend therapiert werden.	
	Literatur: [320, 321]	
	Starker Konsens	

Evidenzbasis/Referenzen aus Leitlinien:

- [320.] Motzer, R.J., et al., Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med, 2015. 373(19): p. 803-13. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/26406148
- [321.] Choueiri, T.K., et al., Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med, 2015. 373(19): p. 1814-23. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/26406150
- [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

- [323.] Motzer, R.J., et al., Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol, 2013. 14(6): p. 552-62. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/23598172
- [324.] Sternberg, C.N., et al., Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol, 2010. 28(6): p. 1061-8. 325. Escudier, B., et al., Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med, 2007. 356(2): p. 125-34. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/17215530
- [326.] Motzer, R.J., et al., Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet, 2008. 372(9637): p. 449-56. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/18653228
- [327.] Motzer, R.J., et al., Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: an open-label, randomised phase 3 trial. Lancet Oncol, 2014. 15(3): p. 286-96.

Tab. 12: Systemtherapieoptionen gemäß Vortherapie in der Zweitlinientherapie

Therapielinie	Vortherapie	Standard	Option
Zweitlinie	nach Zytokinen	Axitinib	Pazopanib Sorafenib
	nach VEGF-Versagen	Cabozatntinib Nivolumab	Axitinib (nach Sunitinib) Everolimus Lenvatinib+Everolimus
	nach Temsirolimus	Axitinib Cabozantinib Pazopanib Sorafenib Sunitinib	

Sequenztherapie des klarzelligen Nierenzellkarzinoms

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

Evidenzbasis/Referenzen aus Leitlinien:

327. Motzer, R.J., et al., Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: an open-label, randomised phase 3 trial. Lancet Oncol, 2014. 15(3): p. 286-96.
332. Motzer, R.J., et al. Record-3: Phase II randomized trial comparing sequential first-line everolimus (EVE) and second-line sunitinib (SUN) versus first-line SUN and second-line EVE in patients with metastatic renal cell carcinoma (mRCC). in ASCO Annual Meeting Proceedings. 2013.
349. Michel, M.S., et al., SWITCH: A randomized sequential open-label study to evaluate efficacy and safety of sorafenib (SO)/sunitinib (SU) versus SU/SO in the treatment of metastatic renal cell cancer (mRCC). J Clin Oncol (Meeting Abstracts), 2014. 32(4_suppl): p. 393-. PubMed: http://meeting.ascopubs.org/cgi/content/abstract/32/4_suppl/393

Kombinationstherapie des klarzelligen Nierenzellkarzinoms

- Eine Kombinationstherapie mit zwei zielgerichteten Therapien soll derzeit nur innerhalb von klinischen Studien durchgeführt 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

Gallardo E et al, 2018 [5].

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

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

Leitlinienorganisation/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

Second-line treatment in advanced disease

- Nivolumab and cabozantinib have shown increased OS in patients with advanced ccRCC previously treated with antiangiogenics, and are the recommended treatments for these patients. Level of evidence: I. Grade of recommendation: A
- Decisions to use either agent may be based on the expected toxicity and on contraindications for each drug, as randomized data is lacking. Level of evidence: IV. Grade of recommendation: D
- Lenvatinib in combination with everolimus has shown increased OS in patients with advanced ccRCC in a randomized phase II trial, and is another valid alternative for these patients. Level of evidence: II. Grade of recommendation: B
- Axitinib and everolimus have not shown increased OS after prior antiangiogenic therapy and should not be used before the previous agents. Nevertheless they may remain acceptable options following such agents, although they have not been tested in randomized trials in this setting. Level of evidence: II. Grade of recommendation: B

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- 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.
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Second-line treatment in advanced disease:

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Ljungberg B et al, 2017 [22].

European Association of Urology (EAU)

Guidelines on renal cell carcinoma.

Leitlinienorganisation/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]

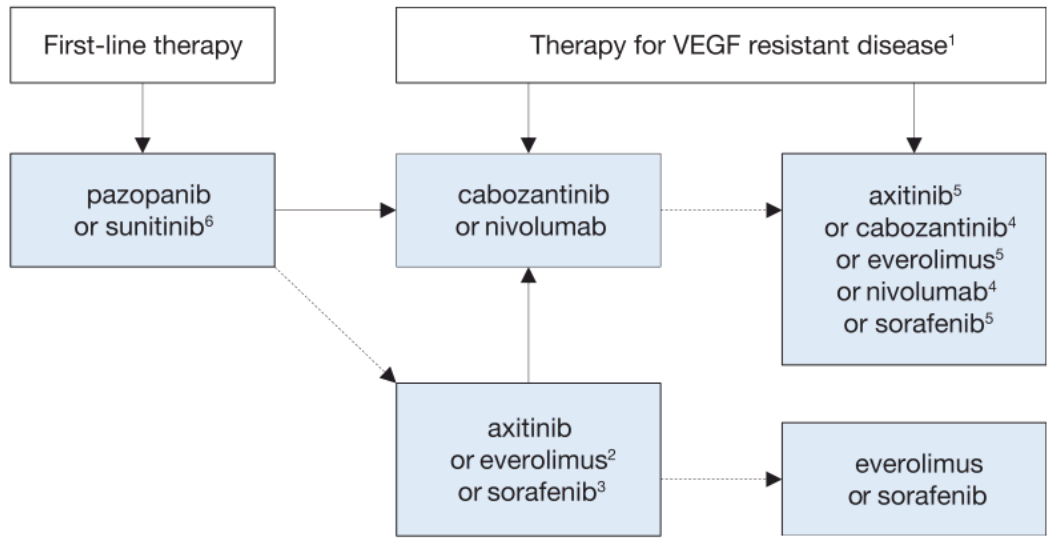
- IL-2 has more side-effects than IFN-α. [LE: 2]
- High dose (HD)-IL-2 is associated with durable complete responses in a limited number of patients. However, no clinical factors or biomarkers exist to accurately predict a durable response in patients treated with HD-IL-2. [LE: 1b]
- Bevacizumab plus 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 [12]

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

Leitlinienorganisation/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 vernknüpft
- Studienqualität bewertet, aber nicht mit der Empfehlung verknüpft
- CoI offengelegt

Empfehlungen

Erstlinie

- Either of the vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGF TKIs) sunitinib or pazopanib is recommended for previously untreated patients with locally advanced or mRCC.

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

Interpretation of Evidence for Recommendation

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

Key Evidence

[5] Escudier B, Bellmunt J, Negrier S, Bajetta E, Melichar B, Bracarda S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. Journal of Clinical Oncology. 2010;28(13):2144-50.
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[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.
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[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.

Zweitlinie nach Zytokin-Therapie

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

Interpretation of Evidence for Recommendation

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

Key Evidence

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

[13)] 20.Leung HWC, Chan ALF, Lin SJ. Indirect comparisons of efficacy and safety between seven newer targeted agents for metastatic renal cell carcinoma: A network meta-analysis of randomised clinical trials. Molecular and Clinical Oncology. 2014;2(5):858-64.

[14)] 22.Michel MS, Vervenne W, De Santis M, Von Weikersthal LF, Goebell PJ, Lerchenmueller J, et al. SWITCH: A randomized sequential open-label study to evaluate efficacy and safety of sorafenib (SO)/sunitinib (SU) versus SU/SO in the treatment of metastatic renal cell cancer (mRCC). Journal of Clinical Oncology. 2014;1).

Benahmed N et al, 2015 [3].

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.
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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.
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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.
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Zweitlinie nach Zytokin-Therapie

Recommedations

- Sorafenib can be considered as second-line treatment in clear cell metastatic renal cell carcinoma. (SoR Strong, LoE High)
- Pazopanib, sunitinib or sorafenib can be considered in metastatic renal cell carcinoma patients previously treated with cytokines (IFN-α, IL-2). (SoR Strong, LoE Low)
- Everolimus can be considered in metastatic renal cell carcinoma patients previously treated with Vascular endothelial growth factor (VEGF)-pathway targeted therapy (i.e. bevacizumab, sunitib, sorafenib) or cytokines (IFN-α, IL-2). (SoR Strong, LoE Low)
- Axitinib is recommended in metastatic renal cell carcinoma patients previously treated with VEGF-pathway targeted therapy or cytokines. (SoR Strong, LoE Low)

- Note: Axitinib is reimbursed after a failure of first line treatment with TKI or cytokine.

Schlussfolgerungen aus dem Review

- Sorafenib improves PFS and CBR in comparison with placebo in low or intermediate risk mRCC patients. This advantage is also observed in sub-population such as elderly, prior cytokine treated patients. In addition, HRQoL is better rated by CC mRCC patients treated with sorafenib than by those treated with placebo whatever the patients' age (< 70 years vs ≥ 70 years).
- After cytokine treatment or in naïve patients, PFS, response rate are improved in CC mRCC patients treated with pazopanib in comparison to those treated with placebo. However, OS and HRQoL are not improved with this TKI.
- After IL-2, Bevacizumab (10 mg/kg or 3 mg/kg) improves PFS and OS in CC mRCC patients in comparison with placebo.
- After previous treatment with sunitinib, bevacizumab plus IFN-α, temsirolimus or cytokine, Axitinib improved PFS in comparison with Sorafenib in CC mRCC but no statistically significant difference in OS and QoL is observed.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 11.04.2018

#	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 tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or sarcoma* or malign*):ti,ab,kw
4	#2 and #3
5	(hypernephroma* or rcc):ti,ab,kw
6	#1 or #4 or #5
7	#6 Publication Year from 2013 to 2018

SR, HTAs in Medline (PubMed) am 12.04.2018

#	Suchfrage
1	((((("carcinoma, renal cell/drug therapy"[MeSH Terms] OR "carcinoma, renal cell/radiotherapy"[MeSH Terms] OR "carcinoma, renal cell/therapy"[MeSH Terms]))))
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]
4	hypernephroma*[tiab] OR rcc[tiab]
5	(#2 AND #3) OR #4
6	((((((((((treatment*[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 treating[tiab]) OR treated[tiab]) OR management[tiab]) OR drug*[tiab]
7	#5 AND #6
8	#1 OR #7
9	(#8) AND ((Meta-Analysis[ptyp] OR systematic[sb] 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]))))))
10	(#9) AND ("2013/04/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp])

Gemeinsamer Bundesausschuss

Leitlinien in Medline (PubMed) am 12.04.2018

#	Suchfrage
1	carcinoma, renal cell[MeSH Terms]
2	Kidney Neoplasms[Mesh:NoExp]
3	(renal[tiab] AND cell[tiab]) OR kidney*[tiab] OR nephroid*[tiab] OR hypernephroid*[tiab] OR grawitz*[tiab] OR collecting duct[tiab]
4	(((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]
5	#3 AND #4
6	hypernephroma*[tiab] OR rcc[tiab]
7	#1 OR #2 OR #5 OR #6
8	(Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[ti] OR recommendation*[ti]) NOT (letter[ptyp] OR comment[ptyp]))
9	#7 AND #8
10	(#9) AND ("2013/04/01"[PDAT] : "3000"[PDAT])

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Anhang

Edwards SJ et al, 2018 [4].

TABLE 5 Summary of Cochrane risk-of-bias assessment for RCTs

Criteria	Study			
	AXIS[43]	Checkmate-025[54]	METEOR[57]	RECORD-1[53]
General risk of bias				
Sources of bias related to study characteristics				
Random sequence allocation	✓	✓	✓	✓
Allocation concealment	✓	✓	✓	✓
Blinding: participant and personnel	✗	✗	✗	✓
Outcome specific				
PFS				
Blinding: outcome assessment	✓	✗	✓	✓
Incomplete outcome data	✓	✓	?	✓
Selective reporting	✓	✓	✓	✓
Other biases	?	?	N/A	?
Overall survival				
Blinding: outcome assessment	✓	✓	✓	✓
Incomplete outcome data	✓	?	?	✓
Selective reporting	✓	✓	✓	✓
Other biases	✓	✓	?	?

TABLE 5 Summary of Cochrane risk-of-bias assessment for RCTs (*continued*)

Criteria	Study			
	AXIS[43]	Checkmate-025[54]	METEOR[57]	RECORD-1[53]
Response rate				
Blinding: outcome assessment	✓	✗	✓	✓
Incomplete outcome data	?	✓	?	✓
Selective reporting	✓	✓	✓	?
Other biases	N/A	N/A	N/A	?
AEs				
Blinding: outcome assessment	✗	✗	✗	✓
Incomplete outcome data	✓	✓	✓	✓
Selective reporting	✓	✓	✓	✓
Other biases	N/A	?	N/A	N/A
HRQoL				
Blinding: outcome assessment	✗	✗	✗	✗
Incomplete outcome data	✓	✓	?	✓
Selective reporting	✓	✓	✓	✗
Other biases	N/A	N/A	N/A	N/A

✗, high risk; ✓, low risk; N/A, not applicable; ?, unclear risk.

TABLE 6 Summary of ROBINS-I risk-of-bias assessments in non-randomised studies

	Study									
	Calvani *et al.*, 2013[58]	ESPN[55]	Iacovelli *et al.*, 2015[59]	Paglino *et al.*, 2013[60]	Porta *et al.*, 2011[61]	SWITCH[56]	Vogelzang *et al.*, 2014[62]		Wong *et al.*, 2014[63]	
Outcome	PFS	PFS	OS	PFS	PFS	PFS	PFS	OS	PFS	OS
Confounding	✗	✗	✗	✗✗	✗✗	✗	~	~	~	~
Selection	✗	~	✗	✗	✗	~	✗	✗	✗	✗
Intervention classification	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Intervention deviations	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Missing data	~	✓	✓	NI	NI	✓	✓	✓	✗	✗
Outcome measures	✗	✓	✓	✗	✗	✗	✗	✓	✗	✓
Outcome reporting	~	✓	✓	~	~	~	✗	✓	✗	✓
Overall judgement	✗	✗	✗	✗✗	✗✗	✗	✗	✗	✗	✗

✗✗, critical risk; ✓, low risk; ~, moderate risk; NI, no information; ✗, serious risk.

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

Pembrolizumab in Kombination mit Axitinib
zur Erstlinienbehandlung des fortgeschrittenen Nierenzellkarzinoms

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 zulassungsüberschreiten-den 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:	
Pembrolizumab L01XC18 KEYTRUDA® Axitinib L01XE17 Inlyta®	<u>Zugelassenes Anwendungsgebiet:</u> KEYTRUDA ist in Kombination mit Axitinib zur Erstlinienbehandlung des fortgeschrittenen Nierenzellkarzinoms (RCC) bei Erwachsenen angezeigt (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.
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) − bei Erwachsenen nach vorangegangener zielgerichteter Therapie gegen VEGF (vaskulärer endothelialer Wachstumsfaktor).
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.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Sunitinib L01XE04 Sutent®	Metastasierte Nierenzellkarzinome (mRCC) SUTENT wird bei Erwachsenen zur Behandlung fortgeschrittener/ metastasierter Nierenzellkarzinome (mRCC) eingesetzt.
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: 2018-B-265-z

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	28. November 2018

Gemeinsamer Bundesausschuss

Inhaltsverzeichnis

Gemeinsamer Bundesausschuss

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

„Behandlung des fortgeschrittenen Nierenzellkarzinoms bei Erwachsenen“

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Nierenzellkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 23.04.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1272 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 27 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

G-BA, 2018 [10].

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 [20].

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 [11].

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 (Neubewertung nach Fristablauf) vom 5. April 2018

Siehe auch IQWiG, 2017 [16,17]

Anwendungsgebiet (laut Zulassung vom 9. September 2016):

CABOMETYX™ ist indiziert (renal cell für die Behandlung des fortgeschrittenen Nierenzellkarzinoms carcinoma, RCC) bei Erwachsenen nach vorangegangener zielgerichteter Therapie gegen VEGF (vaskulärer endothelialer Wachstumsfaktor)

Zweckmäßige Vergleichstherapie:

Nivolumab oder Everolimus

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Everolimus:

Hinweis auf einen geringen Zusatznutzen.

G-BA, 2017 [7].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Axitinib (Ablauf der Befristung) vom 21. September 2017

Siehe auch IQWiG, 2017 [15].

Anwendungsgebiet (laut Zulassung vom 3. September 2012):

Inlyta ist angezeigt zur Behandlung des fortgeschrittenen Nierenzellkarzinoms (renal cell cancer, RCC) bei erwachsenen Patienten nach Versagen von vorangegangener Therapie mit Sunitinib oder einem Zytokin.

a) Nach vorangegangener Therapie mit Sunitinib:

Zweckmäßige Vergleichstherapie:

Nivolumab oder Everolimus

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Nivolumab

Ein Zusatznutzen ist nicht belegt.

b) Nach vorangegangener Therapie mit einem Zytokin:

Zweckmäßige Vergleichstherapie:

Sorafenib

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Sorafenib:

Anhaltspunkt für einen geringen Zusatznutzen.

G-BA, 2017 [8].

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 – Lenvatinib (neues Anwendungsgebiet: fortgeschrittenes Nierenzellkarzinom)

Siehe auch IQWiG, 2016 [18].

Zugelassenes Anwendungsgebiet (laut Zulassung vom 25. August 2016):

Kisplyx ist indiziert in Kombination mit Everolimus zur Behandlung von erwachsenen Patienten mit fortgeschrittenem Nierenzellkarzinom (renal cell carcinoma, RCC) nach einer vorhergehenden, gegen den vaskulären endothelialen Wachstumsfaktor (VEGF) gerichteten Behandlung.

Zweckmäßige Vergleichstherapie:

Nivolumab oder Everolimus

Fazit / Ausmaß des Zusatznutzens gegenüber Everolimus:

Anhaltspunkt für einen geringen Zusatznutzen.

G-BA, 2016 [9].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Nivolumab (neues Anwendungsgebiet).

Siehe auch IQWiG, 2016 [19]

Zugelassenes Anwendungsgebiet (laut Zulassung vom 04.04.2016):

Nierenzellkarzinom (RCC)

OPDIVO ist als Monotherapie bei Erwachsenen zur Behandlung des fortgeschrittenen Nierenzellkarzinoms nach Vortherapie indiziert.

1) Patienten nach antiangiogenetischer Vortherapie

Zweckmäßige Vergleichstherapie:

Everolimus

Fazit / Ausmaß des Zusatznutzens gegenüber Everolimus

Hinweis auf einen beträchtlichen Zusatznutzen.

2) Patienten nach Vortherapie mit Temsirolimus

Zweckmäßige Vergleichstherapie:

Sunitinib

Fazit / Ausmaß des Zusatznutzens gegenüber Sunitinib

Ein Zusatznutzen ist nicht belegt.

G-BA, 2009 [6].

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 [25].

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.

3.3 Systematische Reviews

Schmidt E et al, 2018 [24].

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 check-list

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.

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.

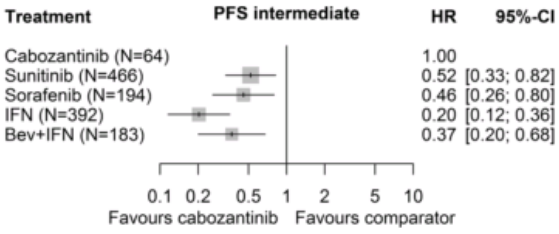

Fig. 2 PFS network meta-analysis forest plots — intermediate-risk group *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: Interferon; *PFS*: progression-free survival

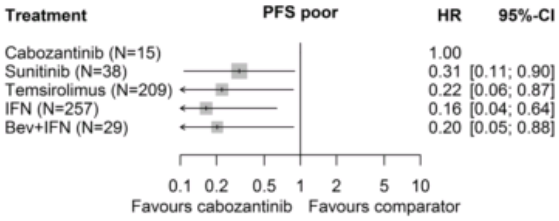

Fig. 3 PFS network meta-analysis forest plots — poor risk-group *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *PFS*: progression-free survival

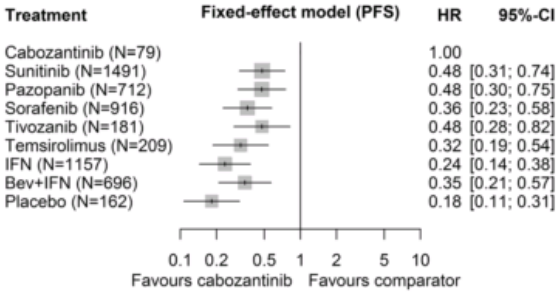

Fig. 4 PFS network meta-analysis forest plots — overall-risk group *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *PFS*: progression-free survival

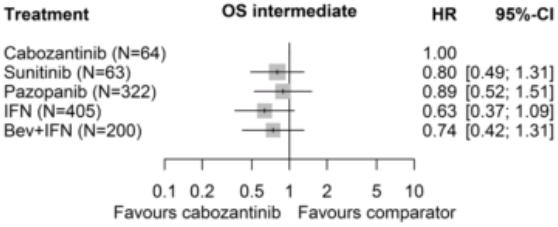

Fig. 5 OS network meta-analysis forest plots — intermediate-risk group. *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *OS*: overall survival

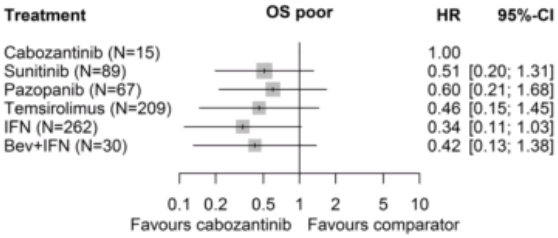

Fig. 6 OS network meta-analysis forest plots — poor-risk group. *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *OS*: overall survival

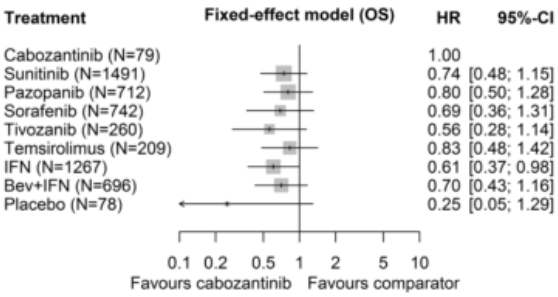

Fig. 7 OS network meta-analysis forest plots — overall-risk group. *Bev*: bevacizumab; *HR*: hazard ratio; *IFN*: interferon; *OS*: overall survival

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.

Wei C et al, 2018 [27].

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 significant 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. 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.

Edwards SJ et al, 2018 [4].

Axitinib, cabozantinib, everolimus, nivolumab, sunitinib and best supportive care in previously treated renal cell carcinoma: a systematic review and economic evaluation.

Fragestellung

- evaluate the clinical effectiveness and cost-effectiveness of axitinib, best supportive care (BSC), cabozantinib, nivolumab, everolimus for treated amRCC in line with their respective marketing authorisations
- identify key areas for further primary and secondary research.

Methodik

Population:

- Patients with previously treated amRCC

Intervention:

For people who have received previous VEGF-targeted therapy:

- axitinib
- cabozantinib
- everolimus
- nivolumab
- sunitinib

Komparator:

- The interventions listed above compared with each other
- BSC

Endpunkte:

- Overall survival
- Progression-free survival
- Response rates
- Adverse events of treatment
- HRQoL

Recherche/Suchzeitraum:

- From inception to 01 and 07/2016

Qualitätsbewertung der Studien:

- Study quality was assessed according to recommendations by the CRD and the Cochrane Handbook for Systematic Reviews of Interventions.
- Study quality for the non-randomised studies was assessed using the Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Twelve studies (n = 4144) met the inclusion criteria: four RCTs (one double-blind RCT and three open-label RCTs) and eight non-RCTs (six retrospective cohort studies and two crossover RCTs in which only second-phase data were relevant).

Charakteristika der Population:

- Populations were predominantly male and white, and the mean age was generally between 60 and 70 years.
- When reported, most patients had stage 3 or 4 clear-cell renal cell carcinoma (RCC) and reasonably good baseline performance status.

Qualität der Studien:

- Siehe Anhang

Studienergebnisse:

- The primary PFS analysis, based on two RCTs (RECORD-1 and METEOR), included cabozantinib, everolimus and BSC and showed statistically significant benefits for cabozantinib and everolimus compared with BSC (HR 0.17, 95% CrI 0.12 to 0.24; and HR 0.33, 95% CrI 0.25 to 0.43, respectively), and for cabozantinib compared with everolimus (HR 0.51, 95% CrI 0.41 to 0.63).
- The primary OS analysis, based solely on RCT data, included cabozantinib, everolimus, nivolumab and BSC, and did not show statistically significant benefits for any treatment
- The primary ORR analysis, based on three RCTs including cabozantinib, everolimus, nivolumab and BSC, showed statistically significant benefits of all treatments compared with BSC.
- Cabozantinib and nivolumab resulted in statistically significant improvements in ORR compared with everolimus (OR 6.67, 95%CrI 3.28 to 12.78; and OR 6.18, 95%CrI 3.75 to

9.84, respectively). The difference between nivolumab and cabozantinib was not statistically significant for ORR compared with BSC.

- Treatments could not be compared using MTC for HRQoL as different measures and tools were used for assessments.

Anmerkung/Fazit der Autoren

The RCT evidence suggests that cabozantinib is likely to be the most effective for PFS and OS, closely followed by nivolumab. All treatments appear to delay disease progression and prolong survival compared with BSC, although the results are heterogeneous. The economic analysis shows that at list price everolimus could be recommended as the other drugs are much more expensive with insufficient incremental benefit. The applicability of these findings to the NHS is somewhat limited because existing confidential patient access schemes could not be used in the analysis. Future work using the discounted prices at which these drugs are provided to the NHS would better inform estimates of their relative cost-effectiveness.

Kommentare zum Review

- Limitations: Treatment comparisons were limited by the small number of RCTs. However, the key limitation of the analysis is the absence of the drug prices paid by the NHS, which was a limitation that could not be avoided owing to the confidentiality of discounts given to the NHS.
- Funding: The National Institute for Health Research Health Technology Assessment programme.

Rousseau B et al, 2016 [23].

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:

- Gemäß Cochrane risk of bias tool

Netzwerk-Metaanalyse

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

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 RCTs / 4282 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

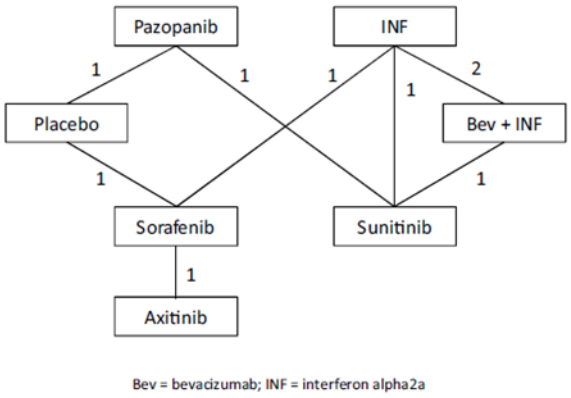

Fig. 3. Network of treatment comparisons established for the nine selected two-arm clinical trials. Lines between agents represent direct comparisons. The numbers represent the number of trial arms providing direct comparison between the angiogenic agents. Bev = bevacizumab; INF = interferon alpha2a.

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.

Anmerkung/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.

Wang L et al., 2015 [26].

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%

Anmerkung/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).

Iacovelli R et al, 2015 [14].

Inhibition of the VEGF/VEGFR pathway improves survival in advanced kidney cancer: a systematic review and meta-analysis.

Fragestellung

The effect of antiangiogenic therapies on overall survival in mRCC patients.

Methodik

Population:

- mRCC patients

Intervention:

- anti-VEGF/VEGFR agent

Komparator:

- non anti-VEGF/VEGFR agent: treatment with placebo or interferon (IFN)

Endpunkt:

- Overall survival (OS)

Recherche/Suchzeitraum:

- 01/2005 to 07/2013

Qualitätsbewertung der Studien:

- Jadad seven-item scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTs / 3469 Patienten

Charakteristika der Population:

- All studies enrolled patients with clear-cell mRCC

Qualität der Studien:

- In all trials, patients were randomly allocated, all were phase III studies, three were double-blind trials.

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

Studienergebnisse:

Wirksamkeit in Bezug auf den Endpunkt "Overall Survival"

Erstlinie

Subpopulation: treatment naïve patients

- Treatment with the anti-VEGF/VEGFR agents decreased the risk of death (HR=0.88; 95%CI, 0.79 – 0.97; *p*=0.010) compared to control (control arm: 1,149 patients: 1,071 received IFN-alph and 78 received placebo). 4 RCT, 2364 patients; keine signifikante Heterogenität (Chi^2=1.31, p=0.73, I^2=0%).
- No differences were found between the anti-VEGFR (TKIs) and the anti-VEGF agents (monoclonal antibody) in terms of the decrease in the risk of death (*p*=0.86).

Zweitlinie

keine Subgruppenanalyse durchgeführt

Anmerkung/Fazit der Autoren

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

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

Iacovelli R et al, 2014 [13].

Targeted therapies and complete responses in first line treatment of metastatic renal cell carcinoma. A meta-analysis of published trials.

Fragestellung

We performed a meta-analysis of published reports about antiangiogenic agents (AA) versus placebo or immunotherapy, focusing on the incidence rates and the relative risk of radiological complete response (CR) in mRCC.

Methodik

Population:

- mRCC patients with good or intermediate prognosis

Intervention:

- Antiangiogenic agents (AAs) (sunitinib, sorafenib, pazopanib, and bevacizumab) as first line of therapy

Komparator:

- non-AAs: INF oder Plazebo

Endpunkt:

complete response (CR)

- Tumor response evaluations were based on Response Evaluation Criteria in Solid Tumors (RECIST)
- Evaluated by investigator and/or independent imaging-review committee

Recherche/Suchzeitraum:

- 01/2000-09/2012

Qualitätsbewertung der Studien:

- Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCT / 2747 Patienten

Charakteristika der Population:

- /

Qualität der Studien:

- For each patient, all imaging scans were evaluated by an independent imaging-review committee (IRC) blinded to study treatment, except for the bevacizumab trials.[5,6] In the latter, only the investigator assessment was performed.
- Randomized treatment allocation sequences were generated in all trials.
- Jadad' score was 3 for three studies and 5 for two studies (Table 1)

Table 1
Main characteristics of the included study.

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

Studienergebnisse:

Wirksamkeit in Bezug auf den Endpunkt “Complete Response”

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

Subgroup analysis by “prognosis”

- No relationships were found between the rates of CRs and the rate of patients with good prognosis (p = 0.27).

Anmerkung/Fazit der Autoren

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

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

Amzal B et al, 2017 [2].

Cabozantinib versus everolimus, nivolumab, axitinib, sorafenib and best supportive care: A network meta-analysis of progression-free survival and overall survival in second line treatment of advanced renal cell carcinoma.

Fragestellung

The objective of the present study is to evaluate progression-free survival (PFS) and overall survival (OS) of cabozantinib compared to everolimus, nivolumab, axitinib, sorafenib, and best supportive care (BSC) in aRCC patients who progressed after previous VEGFR tyrosine-kinase inhibitor (TKI) treatment.

Methodik

Population:

- Patients with renal cell cancer (advanced / metastatic, previously treated)

Intervention:

- Cabozantinib

Komparator:

- Everolimus, axitinib, nivolumab, sorafenib, sunitinib, lenvatinib

Endpunkt:

- PFS
- OS
- Response rates
- Drug discontinuation
- Any other efficacy outcomes
- Safety outcomes
- Quality of life and other Patient-reported Outcomes
- Biomarkers for efficacy and safety

Recherche/Suchzeitraum:

- 06/2016

Qualitätsbewertung der Studien:

- Risk of bias was assessed with an adapted checklist for RCTs as proposed by the Centre for Reviews and Dissemination.

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 studies

Charakteristika der Population:

Anlage I

Qualität der Studien:

- The quality assessment of included trials showed that demographic and baseline characteristics were balanced between the treatment arms in all included studies.
- None of the studies reported unexpected dropouts between study groups.
- All 5 studies reported intent-to-treat (ITT) analysis and reported appropriate method to account for missing data.
- A potential risk of bias arises from investigators, participants and outcome assessors not being blind to treatment allocation in all studies. Effective blinding can ensure that the compared groups receive a similar amount of attention, ancillary treatment and diagnostic investigations.
- Blinding is not always possible, however, and three of the studies were not double blinded

Studienergebnisse:

- The log-normal fixed-effects model displayed the best fit of data for both PFS and OS, and showed that patients on cabozantinib had a higher probability of longer PFS and OS than patients exposed to comparators.
- The survival advantage of cabozantinib increased over time for OS.
- For PFS the survival advantage reached its maximum at the end of the first year's treatment and then decreased over time to zero.

Table 12. Subgroup results–availability of HR results by prognostic score.

End-point	Study	Comparator	Baseline	HR for poor prognosis [95% CI]	HR for intermediate prognosis [95% CI]	HR for favourable prognosis [95% CI]
OS	CheckMate025	Nivolumab	Everolimus	0.47 [0.30, 0.73]	0.76 [0.58, 0.99]	0.89 [0.59, 1.32]
OS	METEOR	Cabozantinib	Everolimus	0.65 [0.39, 1.07]	0.67 [0.48, 0.94]	0.66 [0.46, 0.96]
PFS	AXIS	Axitinib	Sorafenib	0.68 [0.49, 0.94]	0.80 [0.58, 1.10]	0.50 [0.33, 0.76]
PFS	RECORD-1	Everolimus	Placebo	0.44 [0.22, 0.85]	0.32 [0.22, 0.44]	0.31 [0.19, 0.50]
PFS	METEOR	Cabozantinib	Everolimus	0.70 [0.42, 1.16]	0.47 [0.35, 0.62]	0.51 [0.38, 0.69]

Table 13. Sources of OS (ITT), OS (cross-over adjusted), PFS IRC-, and PFS INV-assessed KM plots and hazard ratio results.

HR (95% confidence interval)	OS ITT	OS Cross-over adjusted	PFS Independent review committee (IRC)	PFS Investigator assessed (INV)
METEOR	0.66 (0.53–0.83) Patient level data (published in Fig 2 [14])	Not applicable	0.51 (0.41–0.62) Patient level data (published in Fig 4 [14])	Not applicable
RECORD-1	0.87 (0.65–1.15) Fig 6A [20]	0.60 (0.22–1.65) Fig 5	0.30 (0.22–0.40) Fig 2 [45]	Not applicable, IRC PFS available
CheckMate025	0.73 (0.57–0.93) Fig 1 [14]	Not applicable	Not available	0.88 (0.75–1.03) Fig 2B [14]
TARGET	0.88 (0.74–1.04) Fig1A [21]	Fig 1B [21]	0.44 (0.35–0.55) Fig 2C [47]	Not applicable, IRC PFS available
AXIS**	0.997 (0.78–1.27) Fig 2B [46]	Not applicable	0.741 (0.573–0.958) Fig 2C [22]	Not applicable, IRC PFS available

Key: OS, overall survival; ITT, intention to treat; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; KM, Kaplan-Meier; INV, investigator assessed; IRC, independent review committee assessed.

Note

** prior-sunitinib group results used in the analyses.

Anmerkung/Fazit der Autoren

With all five families of distributions, cabozantinib was superior to all its comparators with a higher probability of longer PFS and OSduring the analyzed 3 years, except with the Gompertz model, where nivolumab was preferred after 24 months.

Albiges L et al, 2015 [1].

EAU – European Association of Urology

A Systematic Review of Sequencing and Combinations of Systemic Therapy in Metastatic Renal Cancer.

Fragestellung

To systematically review relevant literature comparing the clinical effectiveness and harms of different sequencing and combinations of systemic targeted therapies for mRCC.

Methodik

Population:

- keine näheren Angaben

Intervention:

- combining or sequencing systemic targeted therapies

Komparator:

- aktive Substanz oder Placebo

Endpunkt:

- Primary endpoints: PFS, OS

Recherche/Suchzeitraum:

- the original EAU search was updated (covering the period from January 1, 2000, to September 30, 2013) methods protocol of the European Association of Urology (EAU) renal cell carcinoma 2013 guidelines was used as a basis for the search strategy
- Datenbanken: Medline, Medline In- Process, Embase, Cochrane Controlled Trials Register (Cochrane Library, Issue 8, 2013), and the Latin American and Caribbean Center on Health Sciences Information System. The search was complemented by additional sources including systematic reviews from the Cochrane Database of Systematic Reviews (Cochrane Library, Issue 8, 2013), recent conference proceedings of the American Society of Clinical Oncology and European Society of Medical Oncology, ongoing trials from clinicaltrials.gov and the World Health Organisation International Clinical Trials Registry

Qualitätsbewertung der Studien:

- Gemäß Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- n=24 RCTs (n= 9589 Patienten) für qualitative Betrachtung, n=4 für metaanalytische Auswertung

Charakteristika der Population:

- keine näheren Angaben

Qualität der Studien:

- RoB: There were generally low risks of bias across studies; however, clinical and methodological heterogeneity prevented pooling of data for most studies.

Studienergebnisse:

Cytokine pretreated patients

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

- Sunitinib, or other VEGF/VEGFR inhibiting therapies, have widely become the standard of care in the first-line setting.

post-VEGF/VEGFR inhibition setting

- studies investigating sequencing beyond the first-line setting had broad inclusion criteria and no stratification based on prognostic criteria!
- RCTs support the use of both mTOR inhibitors and VEGFR inhibition in the VEGFR TKI–resistant setting.
- AXIS trial is the only RCT comparing two TKIs (axitinib vs. sorafenib) following first-line VEGF inhibition: difference in PFS was significant in the favour of axitinib versus sorafenib, the gain in PFS was short, and no difference in OS was detected in the final analysis.
- INTORSECT study: direct comparison between different classes of agents (temsirolimus, ie, an mTOR inhibitor, vs sorafenib, ie, a VEGFR TKI) following progression on sunitinib, but it failed to define an optimal sequence because there was no statistical significant difference in PFS.
- RECORD-1 phase 3 RCT, designed to evaluate the mTOR inhibitor everolimus as second-line treatment versus placebo, have to be interpreted with caution because only 21% of the patients (53% received two previous treatments including one VEGFR inhibition plus cytokine) were purely second-line post sunitinib.

Kurzzusammenfassung der Studien siehe Table 1:

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

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

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

Anmerkung/Fazit der Autoren

Summarizing the available evidence, it can be concluded that both everolimus and axitinib are valid options after first-line VEGF/VEGFR inhibition failure. Sorafenib, in view of the recent OS results of the INTORSECT trial, might be considered as an alternative option. However, current PFS of second-line treatment is limited, with a median of 4–5 mo.mmentare zum Review

Kommentare zum Review
RCTs hatten häufig inhomogen vorbehandelte Studienpopulationen, siehe Tabelle 1 (oben); Aussagen sind somit einem hohen Verzerrungsrisiko unterworfen.

3.4 Leitlinien

Leitlinienprogramm Onkologie, 2017 [21].

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)

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

GoR

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

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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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

Zweitlinientherapie:

7.6.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **A**	Nach Versagen einer VEGF-basierten Therapie soll die Folgetherapie aus Nivolumab oder Cabozantinib bestehen. Eine spezifische Sequenz der Substanzen kann nicht empfohlen werden.	
Level of Evidence **1b**	Literatur: [320, 321]	
	Starker Konsens	

7.7.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **0**	Nach Versagen von Nivolumab oder Cabozantinib kann auf die jeweils andere Substanz gewechselt werden.	
Level of Evidence **4**	Literatur: [320, 321]	
	Starker Konsens	

7.8.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **0**	Nach Versagen eines VEGF Inhibitors kann die Kombination aus Lenvatinib + Everolimus zur Zweitlinienbehandlung eingesetzt werden.	
1-	Literatur: [322]	
	Starker Konsens	

7.9.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad **0**	In der Zweitlinientherapie nach Sunitinib oder Zytokinen kann Axitinib verwendet werden.	
Level of Evidence **1+**	Literatur: [323]	
	Starker Konsens	

7.10.	Evidenzbasierte Empfehlung	2015
Empfehlungsgrad 0	In der Zweitlinientherapie nach Zytokinen können Sorafenib oder Pazopanib als Alternative zu Axitinib eingesetzt werden.	
Level of Evidence 1+	Literatur: [324, 325]	
	Konsens	

7.11.	Evidenzbasierte Empfehlung	2017
Empfehlungsgrad 0	Nach Versagen von mindestens einem VEGF-Inhibitor kann Everolimus eingesetzt werden.	
Level of Evidence 1+	Literatur: [326]	
	Starker Konsens	

7.12.	Evidenzbasierte Empfehlung	2015
Empfehlungsgrad 0	Nach Versagen eines mTOR-Inhibitors kann die Folgetherapie mittels eines Tyrosinkinaseinhibitors (TKI) erfolgen.	
Level of Evidence 2	Literatur: [327]	
	Konsens	

7.13.	Evidenzbasiertes Statement	2017
Level of Evidence 4	Patienten, die eine Therapie mit Nivolumab erhalten sollen engmaschig und bis zu 12 Monate nach Therapieende auf immunvermittellte Nebenwirkungen kontrolliert werden. Treten Immuntherapie-assoziierte Nebenwirkungen auf, sollen diese umgehend therapiert werden.	
	Literatur: [320, 321]	
	Starker Konsens	

Evidenzbasis/Referenzen aus Leitlinien:

- [320.] Motzer, R.J., et al., Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med, 2015. 373(19): p. 803-13. PubMed: http://www.ncbi.nlm.nih.gov/pubmed/26406148
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Tab. 12: Systemtherapieoptionen gemäß Vortherapie in der Zweitlinientherapie

Therapielinie	Vortherapie	Standard	Option
Zweitlinie	nach Zytokinen	Axitinib	Pazopanib Sorafenib
	nach VEGF-Versagen	Cabozatntinib Nivolumab	Axitinib (nach Sunitinib) Everolimus Lenvatinib+Everolimus
	nach Temsirolimus	Axitinib Cabozantinib Pazopanib Sorafenib Sunitinib	

Sequenztherapie des klarzelligen Nierenzellkarzinoms

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

Evidenzbasis/Referenzen aus Leitlinien:

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

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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
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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

Gallardo E et al, 2018 [5].

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

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

Leitlinienorganisation/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

Second-line treatment in advanced disease

- Nivolumab and cabozantinib have shown increased OS in patients with advanced ccRCC previously treated with antiangiogenics, and are the recommended treatments for these patients. Level of evidence: I. Grade of recommendation: A
- Decisions to use either agent may be based on the expected toxicity and on contraindications for each drug, as randomized data is lacking. Level of evidence: IV. Grade of recommendation: D
- Lenvatinib in combination with everolimus has shown increased OS in patients with advanced ccRCC in a randomized phase II trial, and is another valid alternative for these patients. Level of evidence: II. Grade of recommendation: B
- Axitinib and everolimus have not shown increased OS after prior antiangiogenic therapy and should not be used before the previous agents. Nevertheless they may remain acceptable options following such agents, although they have not been tested in randomized trials in this setting. Level of evidence: II. Grade of recommendation: B

Referenzen aus Leitlinien

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- 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.
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- 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.

Second-line treatment in advanced disease:

- 37. 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;373:1803–13.
- 38. Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373:1814–23.

- 39. Motzer RJ, Hutson TE, Glen H, Michaelson MD, Molina A, Eisen T, 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;16:1473–82.
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- 41. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356:125–34.
- 42. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008;372:449–56.

Ljungberg B et al, 2017 [22].

European Association of Urology (EAU)

Guidelines on renal cell carcinoma.

Leitlinienorganisation/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]

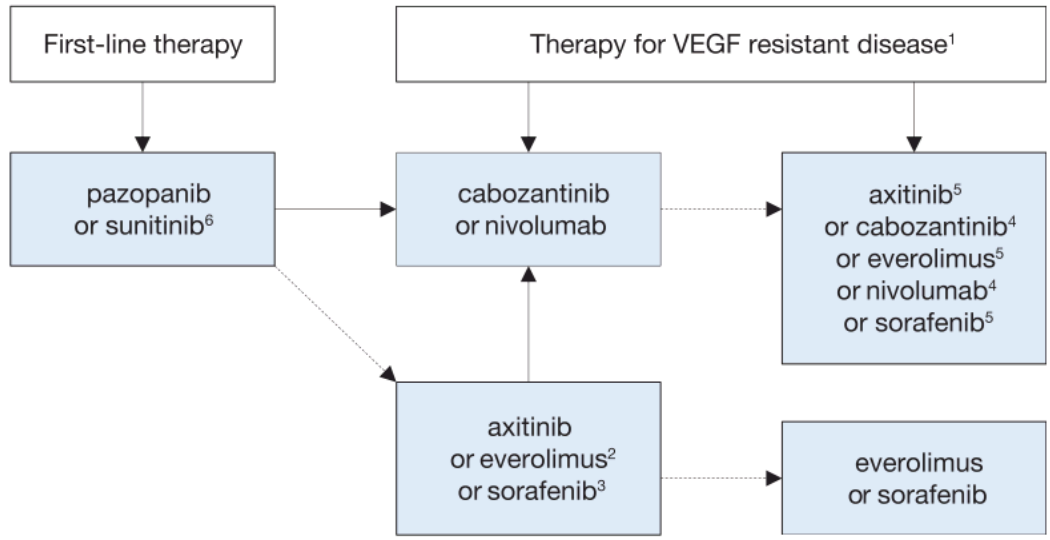
- Cytokine combinations, with or without additional chemotherapy, do not improve OS compared with monotherapy. [LE: 1b]
- Nivolumab leads to superior OS compared to everolimus in patients failing one or two lines of VEGF-targeted therapy. [LE: 1b]

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 [12]

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

Leitlinienorganisation/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 vernknüpft
- Studienqualität bewertet, aber nicht mit der Empfehlung verknüpft
- CoI offengelegt

Empfehlungen

Erstlinie

- Either of the vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGF TKIs) sunitinib or pazopanib is recommended for previously untreated patients with locally advanced or mRCC.

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.
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[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.
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[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.

Zweitlinie nach Zytokin-Therapie

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

Interpretation of Evidence for Recommendation

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

Key Evidence

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

Recommedations

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

Schlussfolgerungen aus dem Review

- Sorafenib improves PFS and CBR in comparison with placebo in low or intermediate risk mRCC patients. This advantage is also observed in sub-population such as elderly, prior cytokine treated patients. In addition, HRQoL is better rated by CC mRCC patients treated with sorafenib than by those treated with placebo whatever the patients' age (< 70 years vs ≥ 70 years).
- After cytokine treatment or in naïve patients, PFS, response rate are improved in CC mRCC patients treated with pazopanib in comparison to those treated with placebo. However, OS and HRQoL are not improved with this TKI.
- After IL-2, Bevacizumab (10 mg/kg or 3 mg/kg) improves PFS and OS in CC mRCC patients in comparison with placebo.
- After previous treatment with sunitinib, bevacizumab plus IFN-α, temsirolimus or cytokine, Axitinib improved PFS in comparison with Sorafenib in CC mRCC but no statistically significant difference in OS and QoL is observed.

Evidenzbasis

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 11.04.2018

#	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 tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or sarcoma* or malign*):ti,ab,kw
4	#2 and #3
5	(hypernephroma* or rcc):ti,ab,kw
6	#1 or #4 or #5
7	#6 Publication Year from 2013 to 2018

SR, HTAs in Medline (PubMed) am 12.04.2018

#	Suchfrage
1	((((("carcinoma, renal cell/drug therapy"[MeSH Terms] OR "carcinoma, renal cell/radiotherapy"[MeSH Terms] OR "carcinoma, renal cell/therapy"[MeSH Terms]))))
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]
4	hypernephroma*[tiab] OR rcc[tiab]
5	(#2 AND #3) OR #4
6	((((((((((treatment*[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 treating[tiab]) OR treated[tiab]) OR management[tiab]) OR drug*[tiab]
7	#5 AND #6
8	#1 OR #7
9	(#8) AND ((Meta-Analysis[ptyp] OR systematic[sb] 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]))))))
10	(#9) AND ("2013/04/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp])

Gemeinsamer Bundesausschuss

Leitlinien in Medline (PubMed) am 12.04.2018

#	Suchfrage
1	carcinoma, renal cell[MeSH Terms]
2	Kidney Neoplasms[Mesh:NoExp]
3	(renal[tiab] AND cell[tiab]) OR kidney*[tiab] OR nephroid*[tiab] OR hypernephroid*[tiab] OR grawitz*[tiab] OR collecting duct[tiab]
4	(((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]
5	#3 AND #4
6	hypernephroma*[tiab] OR rcc[tiab]
7	#1 OR #2 OR #5 OR #6
8	(Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[ti] OR recommendation*[ti]) NOT (letter[ptyp] OR comment[ptyp]))
9	#7 AND #8
10	(#9) AND ("2013/04/01"[PDAT] : "3000"[PDAT])

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Anhang

Edwards SJ et al, 2018 [4].

TABLE 5 Summary of Cochrane risk-of-bias assessment for RCTs

Criteria	Study			
	AXIS[43]	Checkmate-025[54]	METEOR[57]	RECORD-1[53]
General risk of bias				
Sources of bias related to study characteristics				
Random sequence allocation	✓	✓	✓	✓
Allocation concealment	✓	✓	✓	✓
Blinding: participant and personnel	✗	✗	✗	✓
Outcome specific				
PFS				
Blinding: outcome assessment	✓	✗	✓	✓
Incomplete outcome data	✓	✓	?	✓
Selective reporting	✓	✓	✓	✓
Other biases	?	?	N/A	?
Overall survival				
Blinding: outcome assessment	✓	✓	✓	✓
Incomplete outcome data	✓	?	?	✓
Selective reporting	✓	✓	✓	✓
Other biases	✓	✓	?	?

TABLE 5 Summary of Cochrane risk-of-bias assessment for RCTs (*continued*)

Criteria	Study			
	AXIS[43]	Checkmate-025[54]	METEOR[57]	RECORD-1[53]
Response rate				
Blinding: outcome assessment	✓	✗	✓	✓
Incomplete outcome data	?	✓	?	✓
Selective reporting	✓	✓	✓	?
Other biases	N/A	N/A	N/A	?
AEs				
Blinding: outcome assessment	✗	✗	✗	✓
Incomplete outcome data	✓	✓	✓	✓
Selective reporting	✓	✓	✓	✓
Other biases	N/A	?	N/A	N/A
HRQoL				
Blinding: outcome assessment	✗	✗	✗	✗
Incomplete outcome data	✓	✓	?	✓
Selective reporting	✓	✓	✓	✗
Other biases	N/A	N/A	N/A	N/A

✗, high risk; ✓, low risk; N/A, not applicable; ?, unclear risk.

TABLE 6 Summary of ROBINS-I risk-of-bias assessments in non-randomised studies

	Study									
	Calvani *et al.*, 2013[58]	ESPN[55]	Iacovelli *et al.*, 2015[59]	Paglino *et al.*, 2013[60]	Porta *et al.*, 2011[61]	SWITCH[56]	Vogelzang *et al.*, 2014[62]		Wong *et al.*, 2014[63]	
Outcome	PFS	PFS	OS	PFS	PFS	PFS	PFS	OS	PFS	OS
Confounding	✗	✗	✗	✗✗	✗✗	✗	~	~	~	~
Selection	✗	~	✗	✗	✗	~	✗	✗	✗	✗
Intervention classification	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Intervention deviations	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Missing data	~	✓	✓	NI	NI	✓	✓	✓	✗	✗
Outcome measures	✗	✓	✓	✗	✗	✗	✗	✓	✗	✓
Outcome reporting	~	✓	✓	~	~	~	✗	✓	✗	✓
Overall judgement	✗	✗	✗	✗✗	✗✗	✗	✗	✗	✗	✗

✗✗, critical risk; ✓, low risk; ~, moderate risk; NI, no information; ✗, serious risk.