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ORIGINAL ARTICLE

Second-line treatment for metastatic clear cell renal cell cancer: experts' consensus algorithms

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Abstract
Background Second-line systemic treatment options for metastatic clear cell renal cell cancer (mccRCC) are diverse and treatment strategies are variable among experts. Our aim was to investigate the approach for the second-line treatment after first-line therapy with a tyrosine kinase inhibitor (TKI). Recently two phase III trials have demonstrated a potential role for nivolumab (NIV) and cabozantinib (CAB) in this setting. We aimed to estimate the impact of these trials on clinical decision making.
Materials and methods Eleven international experts were asked to provide their treatment strategies for second-line systemic therapy for mccRCC in the current setting and once NIV and CAB will be approved and available. The treatment strategies were analyzed with the objective consensus approach.
Results The analysis of the decision trees revealed everolimus (EVE), axitinib (AXI), NIV and TKI switch (sTKI) as therapeutic options after first-line TKI therapy in the current situation and mostly NIV and CAB in the future setting. The most commonly used criteria for treatment decisions were duration of response, TKI tolerance and zugzwang a composite of several related criteria.
Conclusion In contrast to the first-line setting, recommendations for second-line systemic treatment of mccRCC among experts were not as heterogeneous. The agents mostly used after disease progression on a first-line TKI included: EVE, AXI, NIV and sTKI. In the future setting of NIV and CAB availability, NIV was the most commonly chosen drug, whereas several experts identified situations where CAB would be preferred.

Keywords Algorithm · Renal cell cancer · Consensus · Diagnostic nodes

Implications for practice

This patterns of care analysis in the second-line treatment of metastatic renal cell cancer demonstrated variability in

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treatment strategies after first-line tyrosine kinase inhibitors. Once nivolumab and cabozantinib are approved and available, a much higher level of consensus with a clear majority of experts choosing nivolumab for second-line treatment of metastatic clear cell renal cell cancer can be expected.

Introduction

The treatment of metastatic clear cell renal cell cancer (mccRCC) is characterized by abundance of treatment alternatives and relatively little evidence to favor one over the other [1, 2]. Recently a survey among international experts revealed a wide range of treatment recommendations and very little consensus in the first-line setting [3]. There was consensus for active treatment with a tyrosine kinase inhibitor (TKI), specifically sunitinib (SUN) or pazopanib (PAZ), and their selection was mostly dependent on comorbidities (cardiac or hepatic insufficiency) or patient disposition. However, in many situations, other treatment choices were revealed.

Due to the prolonged survival and the inadvertently developing biological resistance, most mccRCC patients receive a second-line treatment. Clinicians can choose from multiple agents, supported by phase III trial data. There is evidence for the activity of subsequent VEGF inhibition with axitinib (AXI) [4] or sorafenib (SOR) [5], or of switching to the mTOR inhibitor everolimus (EVE) [6].

Different study designs, different patient populations (progression on regimens with regulatory approval at the time of study design, refractory to SUN only, progression on SUN and/or SOR, respectively) and only one real head-to-head comparison of AXI and SOR leave the clinician with several treatment options and individual preference, parameters such as toxicity, or reimbursement plans to rely their therapy decision on.

Just recently, the spectrum of treatment options was broadened by the introduction of nivolumab (NIV), an immunotherapeutic agent that inhibits the T cell checkpoint regulator programmed death 1 (PD-1). In a randomized open-label phase III study NIV was compared with EVE in the second-line treatment setting, where it showed a clinically meaningful and significant benefit in terms of overall survival (25 months vs. 19.6 months, 27 % risk reduction), response rate (25 vs. 5 %) and fewer high-grade adverse events (19 vs. 37 %) [7].

Another new therapeutic option is cabozantinib (CAB), a multikinase inhibitor targeting vascular endothelial growth factor receptor (VEGFR), MET, RET and AXL which was recently examined in comparison with EVE in a randomized, open-label phase III trial [8]. With CAB also a benefit in overall survival (21.4 vs. 16.5 months), a 33 % reduction in the risk of death, a longer PFS (7.4 vs. 3.9 months), a higher response rate (17 vs. 3 % per independent review committee) and a similar discontinuation rate due to adverse events (12 vs. 11 %) have been shown in a planned interim analysis [9].

The aim of our investigation was to examine the current level of consensus in second-line systemic treatment among a group of experts [10]. Additionally, we investigated the potential impact that NIV and CAB might have on decision making in the future when readily available.

Methods

Participant selection was based on a previously published investigation in the first-line setting of mccRCC [3]. Participants were asked to describe their treatment strategies in the second-line treatment of mccRCC after first-line treatment with a TKI (SUN or PAZ). Local treatments for oligo-progression (surgery, radiotherapy) were excluded. Patients not fit enough to undergo second-line treatment that would receive best supportive care were also excluded from this analysis.

Next to providing their treatment strategies in the current setting, the participants were also asked to provide their treatment strategies when NIV or CAB will be approved and available.

We also asked the participants to provide the decision criteria for the respective treatment choices.

The treatment strategies and decision criteria were converted into decision trees and re-discussed with the participants. Decision criteria that were used by less than three centers were excluded from the analysis; these are addressed in the discussion. Criteria that had the same meaning were unified to provide compatibility. The decision trees were finalized in February 2016 and then compared using the objective consensus methodology [10] and analyzed for consensus as well as discrepancies as described in other settings [11, 12].

Results

Analysis of the 11 treatment recommendations, in the current as well as in the future setting, revealed four distinct treatment recommendations and three decision criteria.

Current treatment recommendations for the second-line setting after disease progression on a TKI were AXI, EVE, NIV and TKI switch (sTKI). The results are summarized in Table 1.

One decision tree example for the current treatment situation is depicted in Fig. 1.

Among the decision criteria proposed by the experts, several included a need for tumor response owing to

Table 1 Current and future treatment options in second-line therapy by center

Current treatment	Cambridge	Cleveland	Boston	Hannover	London	Oslo	Paris	Pavia	Rome	St. Gallen	Vienna
NIV		■	■								
AXI	■			■	■	■	■	■	■	■	■
EVE	■			■		■	■	■	■	■	
sTKI	■								■		

Future treatment	Cambridge	Cleveland	Boston	Hannover	London	Oslo	Paris	Pavia	Rome	St. Gallen	Vienna
NIV	■	■	■	■	■	■	■	■	■	■	■
AXI	■					■					
CAB	■							■			■

NIV nivolumab, *AXI* axitinib, *EVE* everolimus, *sTKI* second tyrosine kinase inhibitor, *CAB* cabozantinib

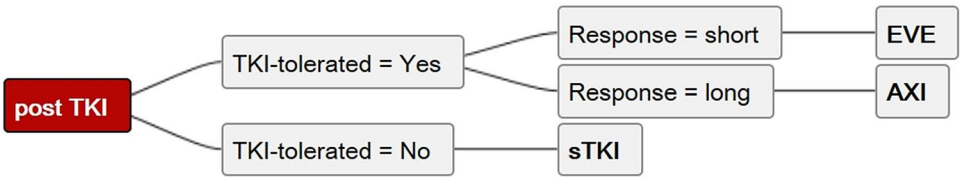

Fig. 1 Sample decision tree in the current setting

the extent of disease or symptoms, or the rate of disease progression. This urgency was expressed differently by the experts (aggressiveness, tumor volume or burden, bulky disease, symptomatic, shrinkage needed, response required) and was summarized under the term "zugzwang." Zugzwang (ZZ) is a German word and implies the compulsion to move [13]. We had introduced this term in our previous publication on first-line treatment in mccRCC [3].

The criteria used to choose treatment in the second-line were: duration of response—long versus short to first-line therapy—however, no clear cutoff was reported, need for response and high tumor burden (ZZ) and TKI tolerability or TKI toxicity (Table 2).

In the current setting, at progression after a long and well-tolerated TKI first-line therapy and now evident ZZ, there was high consensus among the experts (82 %) to choose AXI as second-line therapy and 45 % would choose EVE if the response was ranked as short. In case of poor TKI tolerance in the first-line setting, the analysis showed a high level of disparity among the experts, with 36 % choosing AXI in the short response setting and 55 % choosing AXI in the long response setting. In the absence of ZZ, the level of disparity was even higher. After good TKI tolerance, 64 % would chose AXI in the long response and 36 % would chose EVE in the short response setting. Conversely, after poor TKI tolerance 45 % would choose EVE in the short response and just 36 % AXI in the long response setting. Figure 2 shows the degree of agreement in treatment choice in the current setting.

Two centers considered switching to another TKI (SUN→PAZ or PAZ→SUN) if during first-line TKI treatment drug-specific toxicities prevented treatment continuation. Changes in dose and schedule were also mentioned as second-line therapy options—this was summarized as sTKI. Of note, this strategy was only chosen in patients with treatment response or disease stabilization to the first TKI.

Toxicities to a first-line TKI preventing a specific second-line treatment were excluded from the analysis, e.g., uncontrolled hypertension, cardiac insufficiency for AXI. SOR was mentioned specifically in the setting of uncontrolled hypertension or severe heart problem as an alternative to AXI in one center. Uncontrolled diabetes or diabetes requiring high doses of insulin was mentioned as an exclusion criterion for EVE. Importantly, autoimmune disease is a specific contraindication to NIV due to the mechanism of action, which is also reflected in the label.

In the future setting, nearly all centers would choose NIV as preferred treatment for second-line therapy. However, two centers would choose AXI for patients with ZZ, of whom one center would decide between CAB and AXI depending on the response to first-line treatment and in two centers patients with ZZ would receive CAB instead of NIV due to the experience of early deaths on NIV in aggressive disease (Table 1).

Table 2 Treatment selection criteria by center

Criteria	Cambridge	Cleveland	Boston	Hannover	London	Oslo	Paris	Pavia	Rome	St. Gallen	Vienna
Duration of response	■					■		■	■	■	
Zugzwang (ZZ)	■			■		■	■	■			■
TKI-tolerated	■					■			■		

Decision criteria that were used by less than three centers were excluded from the analysis

TKI tyrosine kinase inhibitor

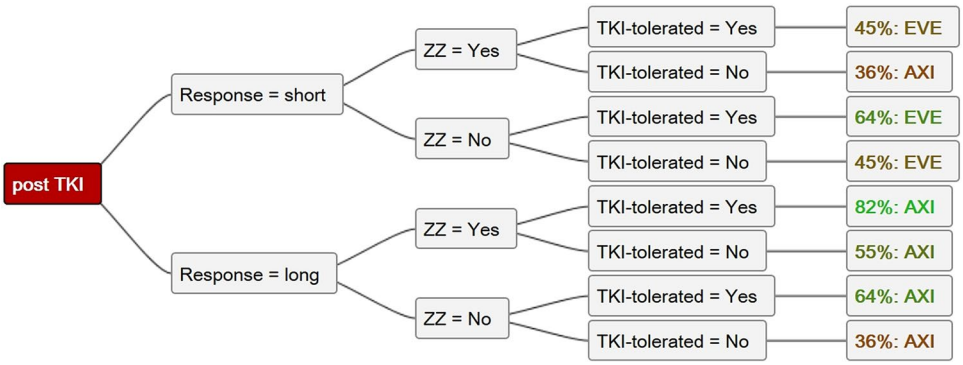

Fig. 2 Most common (mode) recommendations for treatment options in the current setting

Figures 3 and 4 illustrate the decision criteria and treatments by center in the current and future setting, respectively.

Discussion

This report on a comparison of treatment algorithms for mccRCC is the result of a survey among 11 medical experts in the field of RCC. In total, four different treatment options were revealed in the setting of disease progression after a first-line TKI in the current setting, and three in the future setting provided availability of drugs that were recently assessed in clinical trials. Three predominant decision criteria were found: duration of response to first-line TKI treatment, tolerance of this treatment and ZZ.

We identified areas of consensus in these two hypothetical treatment scenarios. In the current treatment setting, a clear majority (82 % of the experts) would choose AXI upon disease progression on a well-tolerated first-line TKI therapy and evident ZZ. Similarly, there was consensus among the experts for patients without ZZ and good TKI tolerance, with a 64 % choice of EVE after a short response and 64 % choice of AXI in case of a long response to a first-line TKI, respectively. In the future scenario, provided ubiquitous availability of NIV and CAB nearly all experts would chose NIV irrespective of ZZ, response duration and TKI tolerability. Only two experts would prefer CAB in the case of ZZ. This is in line with the European Association of Urology (EAU) guidelines on mccRCC, where AXI, EVE, NIV and CAB received a 1b recommendation as a second-line treatment after failure of VEGF-targeted therapy [14]. Just recently the guidelines were updated, mainly driven by the OS data for CAB [9], and confirmed the recommendation for CAB and NIV [15].

Interestingly, none of the experts mentioned the use of lenvatinib (LEN) as single agent or in combination with EVE. The multi-target TKI LEN was recently studied in a three-arm phase II study in the second-line treatment setting after progression on VEGF-targeted therapy and offered a significantly prolonged progression-free survival both as single agent or in combination with EVE compared with EVE alone [16]. However, an investigator-independent radiological review of the data showed no significant difference in progression-free survival between LEN and EVE alone, but confirmed the results for the combination therapy [17]. Reasons for not choosing LEN/EVE could be that this is a randomized phase II trial in contrast to CheckMate 025 and METEOR, which are both phase III trials. In addition, the high degree of grade 3 and 4 adverse events, 79 % on the LEN alone arm and 71 % on the combination arm of LEN and EVE, respectively, may be relevant for omitting these therapies. Of note, the combination of LEN/EVE was approved by the Food and Drug Administration (FDA) on May 13, 2016 [18].

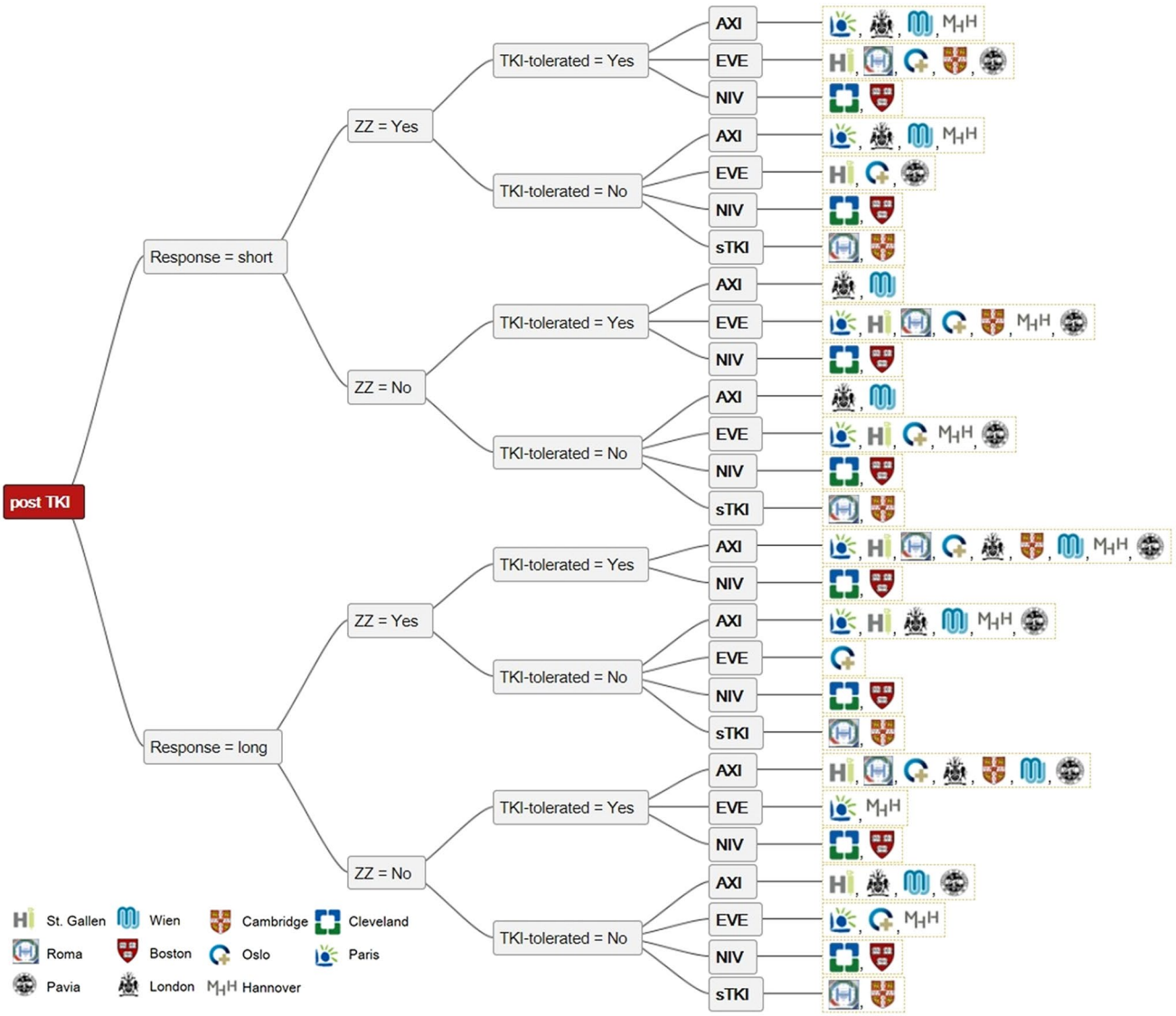

Fig. 3 Decision criteria and treatments by center in the current setting

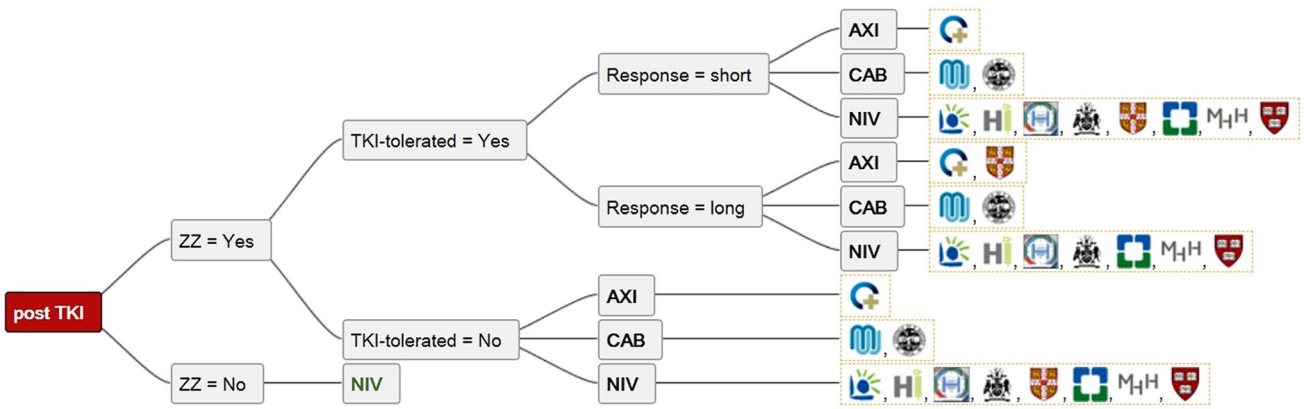

Fig. 4 Decision criteria and treatments by center in the future setting

Despite a long debate and multiple publications on the best choice for the second-line treatment in mccRCC [19], we observed a high degree of consensus among experts. With the availability of NIV, this consensus will be even more apparent. Partially in contrast to second-line treatment strategies in the current clinical setting, the strategies in the future setting, provided NIV and CAB availability, will heavily rely on the use of NIV. Although in certain situations CAB may be an option or even preferred, NIV remains the first-choice treatment in the second-line setting. Despite the higher consensus among experts in comparison with the first-line therapy, the second-line treatment of mccRCC remains complex with many open questions and conflicting areas.

Median progression-free survival was 4.6 months for NIV and 7.4 months for CAB in the pivotal trials, respectively [7, 8]. Hence, there is a need for further treatments, and the question arises which drug should be chosen for third-line treatment. In a recently published retrospective analysis, efficacy and safety of VEGFR-TKIs after PD-1 inhibition were demonstrated [20].

Recent insights into tumor cell biology question not only the standard Response Evaluation Criteria in Solid Tumors (RECIST) progression definition, but offer a possible explanation for the effectivity of continued targeted therapy beyond RECIST progression [21]. This opens the discussion on the crucial and unsolved question when and whether to change treatments. Particularly since actionable immunologic drivers of RCC response are not clear, the most effective duration of therapy with, e.g., NIV and whether the therapy should continue beyond progression remains unknown [22]. There may also be waiting times between lines of treatment, and these are not part of this analysis.

One of the decision criteria used by five of 11 experts was long versus short duration of first-line TKI therapy. Duration of treatment was used as a stratification factor in the Investigating Torisel As Second-Line Therapy (INTORSECT) trial. Patients who had progressed after treatment with SUN were randomized to receive the mTOR inhibitor temsirolimus (TEM) or the TKI SOR.

In an exploratory subgroup analysis of prespecified factors, differential overall survival (OS) benefit with SOR versus TEM was identified: Median OS with SOR was longer in comparison with TEM for patients whose duration of previous treatment with SUN was >180 days (17.8 vs. 14.4 months). For patients on SUN treatment <180 days, no significant difference in OS was observed (11.4 months for SOR vs. 10.1 months for TEM, respectively) [5]. Not all experts made a clear cut distinction between short and long duration of first-line TKI treatment at 6 months, and some provided a time range (e.g., 6–10 months).

Other relevant decision criteria included comorbidities and contraindications for certain drugs, which were excluded from the analysis because they were relevant to fewer than three experts. We had explicitly restricted this survey to patients fit enough to receive a second-line treatment, and therefore, performance status (PS) was not one of the main criteria for drug selection. Both of these procedures represent a certain limitation in applicability to a few specific clinical scenarios; for practical reasons and legibility of the analysis, these restrictions were required. Additionally, for the future setting in one center CAB would only be the choice in the presence of an aggressive disease (ZZ), but still a good PS; in the same setting, but in the presence of a low PS, NIV would be the choice instead. This is not reflected in the decision tree in such detail.

A limitation of this analysis is that authors may have interpreted the question about the decision criteria for the respective treatment choices differently from each other and certain aspects cannot be ascertained with our method, e.g., bad tolerance of first-line TKI may lead to a short response, inasmuch as the dose has to be reduced or the drug stopped completely for toxicity reasons. On the other hand, the response may be short even though the patient manages to keep taking the TKI through significant toxicity.

In the UK setting, this makes a considerable difference, since physicians are allowed to change to an alternative first-line therapy (sTKI) if the original choice is active but poorly tolerated.

Our results pose a conundrum regarding the ethical and practical ramifications of novel expensive therapeutics. Provided affordability, would the recommendation be that patients pay for NIV out of pocket if it is not yet covered by health insurers? This financial issue was not raised within this investigation, yet the problem of reimbursement and costs is a critical issue and the consequences remain to be answered in the near future. The National Institute for Health and Care Excellence (NICE) does not recommend EVE as a second treatment for people with advanced RCC, whereas AXI is recommended as long as the manufacturer provides AXI with the discount agreed in the patient access scheme [23].

Importantly, some of the experts do not necessarily choose a TKI as first-line treatment in mccRCC, but rather HD-IL 2 or interferon and bevacizumab, as outlined in a previous analysis [3].

Currently there are no reliable predictive markers available to guide decision making in the setting of disease progression on or after a TKI.

The results, which are presented here, are neither a recommendation nor a guideline for the treatment of mccRCC patients. The field is evolving quickly, and new data become available; hence, any algorithm in the field of mccRCC may be short lived. Despite this limitation, the information may be helpful for clinicians in everyday

decision making, especially in scenarios where evidence-based medicine is limited [24].

Conclusion

When his study was conducted, the majority of experts would use AXI or EVE in the second-line treatment of mccRCC. When readily available, the most common second-line treatment after first-line TKI will likely receive NIV.

Authors' contributions *C. Rothermundt, J. von Rappard* and *PM. Putora* involved in protocol/project development, data collection and management, data analysis, manuscript writing and editing, primary analysis and interpretation of the data. *T. Eisen, B. Escudier*, *V. Grünwald*, *J. Larkin, D. McDermott, J. Oldenburg*, *C. Porta*, *B. Rini, M. Schmidinger* and *CN. Sternberg* contributed to data collection and management, data analysis, manuscript writing and editing.

Compliance with ethical standards

Conflict of interest *Rothermundt C* Pfizer (Consultant Scientific Advisory Board), GSK (Symposium funding–Personal fees), Novartis (Symposium funding–Personal fees); *von Rappard J* None; *Eisen T* AstraZeneca (Grant-Employment since 01/09/2014), Novartis (Personal Fees), Bayer (Grant), Pfizer (Gant and Personal fees), GSK (Personal fees), Roche (Personal fees), BMS (Personal fees), AVEO (Personal fees–TMG), Astella (Personal fees–TMG); *Escudier B* None; *Grünwald V* Bayer (Personal fees Lecture), GSK (Personal fees Lecture and Advisor), Novartis (Personal fees Lecture and Advisor), Pfizer (Personal fees Lecture and Advisor); *Larkin J* None; *McDermott D* Roche (Personal fees), Pfizer (Personal fees), BMS (Personal fees), Merck (Personal fees); *Oldenburg J* None; *Porta C* Pfizer (Grant and personal fees), GSK (Personal fees), Bayer (Personal fees), Novartis (Grant, personal fees and non-financial support), Astellas (Grant), Pierre Fabre (Grant); *Rini B* Pfizer (Consulting and research funding); *Schmidinger M* Pfizer (Lectures and consultancy), GSK (Lectures and consultancy), Roche (Lectures and consultancy), Astellas (Lectures and consultancy), Novartis (Lectures and consultancy; *Sternberg C* Pfizer (Honoraria), Novartis (Honoraria); *Putora PM* None.

References

1. Escudier B, Porta C, Schmidinger M, Algaba F, Patard JJ, Khoo V, Eisen T, Horwich A, Group EGW (2014) Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 25(3):49–56. doi:10.1093/annonc/mdu259
2. Ouzaid I, Rini B (2014) Words of wisdom: re: Pazopanib versus sunitinib in metastatic renal-cell carcinoma. Eur Urol 65(3):667–668. doi:10.1016/j.eururo.2013.11.023
3. Rothermundt C, Bailey A, Cerbone L, Eisen T, Escudier B, Gillessen S, Grunwald V, Larkin J, McDermott D, Oldenburg J, Porta C, Rini B, Schmidinger M, Sternberg C, Putora PM (2015) Algorithms in the first-line treatment of metastatic clear cell renal cell carcinoma-analysis using diagnostic nodes. Oncologist 20(9):1028–1035. doi:10.1634/theoncologist.2015-0145
4. Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, Michaelson MD, Gorbunova VA, Gore ME, Rusakov IG, Negrier S, Ou YC, Castellano D, Lim HY, Uemura H, Tarazi J, Cella D, Chen C, Rosbrook B, Kim S, Motzer RJ (2011) Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 378(9807):1931–1939. doi:10.1016/s0140-6736(11)61613-9
5. Hutson TE, Escudier B, Esteban E, Bjarnason GA, Lim HY, Pittman KB, Senico P, Niethammer A, Lu DR, Hariharan S, Motzer RJ (2014) Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. J Clin Oncol 32(8):760–767. doi:10.1200/JCO.2013.50.3961
6. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grunwald V, Thompson JA, Figlin RA, Hollaender N, Kay A, Ravaud A, Group R-S (2010) Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer 116(18):4256–4265. doi:10.1002/cncr.25219
7. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D, Choueiri TK, Gurney H, Donskov F, Bono P, Wagstaff J, Gauler TC, Ueda T, Tomita Y, Schutz FA, Kollmannsberger C, Larkin J, Ravaud A, Simon JS, Xu LA, Waxman IM, Sharma P, CheckMate I (2015) Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 373(19):1803–1813. doi:10.1056/NEJMoa1510665
8. Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, Hammers H, Hutson TE, Lee JL, Peltola K, Roth BJ, Bjarnason GA, Geczi L, Keam B, Maroto P, Heng DY, Schmidinger M, Kantoff PW, Borgman-Hagey A, Hessel C, Scheffold C, Schwab GM, Tannir NM, Motzer RJ (2015) Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med 373(19):1814–1823. doi:10.1056/NEJMoa1510016
9. Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, Hammers HJ, Donskov F, Roth BJ, Peltola K, Lee JL, Heng DY, Schmidinger M, Agarwal N, Sternberg CN, McDermott DF, Aftab DT, Hessel C, Scheffold C, Schwab G, Hutson TE, Pal S, Motzer RJ, investigators M (2016) Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol. doi:10.1016/S1470-2045(16)30107-3
10. Putora PM, Panje CM, Papachristofilou A, Dal Pra A, Hundsberger T, Plasswilm L (2014) Objective consensus from decision trees. Radiat Oncol 9:270. doi:10.1186/s13014-014-0270-y
11. Panje CM, Dal Pra A, Zilli T, RZ D, Papachristofilou A, Herrera FG, Matzinger O, Plasswilm L, Putora PM (2015) Consensus and differences in primary radiotherapy for localized and locally advanced prostate cancer in Switzerland: a survey on patterns of practice. Strahlenther Onkol 191(10):778–786. doi:10.1007/s00066-015-0849-8
12. Hundsberger T, Hottinger AF, Roelcke U, Roth P, Migliorini D, Dietrich PY, Conen K, Pesce G, Hermann E, Pica A, Gross MW, Brugge D, Plasswilm L, Weller M, Putora PM (2016) Patterns of care in recurrent glioblastoma in Switzerland: a multicentre national approach based on diagnostic nodes. J Neurooncol 126(1):175–183. doi:10.1007/s11060-015-1957-0
13. wikipedia zugzwang (2016) https://en.wikipedia.org/wiki/Zugzwang. Accessed 17 Feb 2016
14. Ljungberg B, Bensalah K, Bex A, Canfield S, Dabestani S, Giles RH, Hofmann F, Hora M, Kuczyk MA, Lam T, Marconi L, Merseburger AS, Powles T, Staehler M, Volpe A (2016) Renal cell carcinoma. https://uroweb.org/guideline/renal-cell-carcinoma/?type=pocket-guidelines. Accessed 28 June 2016
15. Powles T, Staehler M, Ljungberg B, Bensalah K, Canfield SE, Dabestani S, Giles RH, Hofmann F, Hora M, Kuczyk MA (2016) European Association of Urology Guidelines for Clear Cell Renal Cancers That Are Resistant to Vascular Endothelial Growth Factor Receptor-Targeted Therapy. European Urology. doi:10.1016/j.eururo.2016.06.009

16. Motzer RJ, Hutson TE, Glen H, Michaelson MD, Molina A, Eisen T, Jassem J, Zolnierek J, Maroto JP, Mellado B, Melichar B, Tomasek J, Kremer A, Kim H-J, Wood K, Dutcus C, Larkin J (2015) Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol 16(15):1473–1482. doi:10.1016/s1470-2045(15)00290-9
17. Motzer RJ, Hutson TE, Ren M, Dutcus C, Larkin J (2016) Independent assessment of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma. Lancet Oncol 17(1):e4–e5. doi:10.1016/s1470-2045(15)00543-4
18. Research CfDEa (2016) Approved drugs—lenvatinib in combination with everolimus. Center for Drug Evaluation and Research. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm501070.htm. Accessed 29 June 2016
19. Fischer S, Gillessen S, Rothermundt C (2015) Sequence of treatment in locally advanced and metastatic renal cell carcinoma. Transl Androl Urol 4(3):310–325. doi:10.3978/j.issn.2223-4683.2015.04.07
20. Nadal R, Amin A, Geynisman DM, Voss MH, Weinstock M, Doyle J, Zhang Z, Viudez A, Plimack ER, McDermott DF, Motzer R, Rini B, Hammers HJ (2016) Safety and clinical activity of vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitors after programmed cell death 1 inhibitor treatment in patients with metastatic clear cell renal cell carcinoma. Ann Oncol Off J Eur Soc Med Oncol ESMO. doi:10.1093/annonc/mdw160
21. Burotto M, Wilkerson J, Stein W, Motzer R, Bates S, Fojo T (2014) Continuing a cancer treatment despite tumor growth may be valuable: sunitinib in renal cell carcinoma as example. PLoS One 9(5):e96316. doi:10.1371/journal.pone.0096316
22. Quinn DI, Lara PN Jr (2015) Renal-cell cancer—targeting an immune checkpoint or multiple kinases. N Engl J Med. doi:10.1056/NEJMe1511252
23. Umeweni N, Mikudina B, Sutcliffe F, Stevens A (2015) NICE guidance on axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment. Lancet Oncol 16(4):367–368. doi:10.1016/s1470-2045(14)70484-x **(Epub 2015 Feb 25)**
24. Putora PM, Oldenburg J (2013) Swarm-based medicine. J Med Internet Res 15(9):e207. doi:10.2196/jmir.2452