Emerging M+ RCC treatments from EAU Guidelines

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SUMMARY

Thanks to our improved understanding of the molecular pathogenesis of metastatic renal cell carcinoma, multiple new treatment agents have appeared and extended our therapeutic possibilities. Novel molecular-targeted agents have vastly replaced cytokine therapies but pointed out new challenges in finding the optimal sequence and/or combination in treating metastatic renal cell carcinoma patients. This review focusses on the emerging therapeutic options according to the European Association of Urology guidelines in the rapidly changing renal cell carcinoma landscape.

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INTRODUCTION

Renal cell carcinoma (RCC) is the 14th most common malignancy in the world, accounting for 3% of all malignancies and 90% of kidney tumours. In the European Union there were approximately 84,000 new cases of RCC and 35,000 deaths due to kidney cancer in 2012.[1] About one third of newly diagnosed cases are metastatic at presentation.[2] Peak incidence is at the age of 60 to 70, with a 1.5:1 male predominance. It appears to be more common in Western countries but prevalence is rising in developing countries. Most important risk factors are smoking, obesity and hypertension.[3] Standard-of-care for localised disease remains complete surgical resection of the tumour. In the metastatic setting, treatment paradigms have been rapidly evolving in the past decade. Cytoreductive surgery still plays a role in the treatment of metastatic RCC (mRCC), but its use decreased since the introduction of targeted therapies (TT). Since 2005 TT such as monoclonal antibodies (nivolumab), vascular endothelial growth factor (VEGF) inhibitors (e.g. sunitinib, sorafenib, pazopanib, axitinib, cabozantinib, bevacizumab), and mammalian target of rapamycine (mTOR) inhibitors (e.g. Temsirolimus, everolimus) have become widely available for clinical use, drastically reducing the use of older immunotherapies such as interferon-α (IFNα) and interleukin-2 (IL-2). New immunotherapies based on immune checkpoint inhibition are currently being investigated in phase III trials. However, the ideal sequence and timing of surgery and TT remains to be decided. The European Association of Urology (EAU) guidelines give a comprehensive overview of this rather complex landscape of systemic therapies, which is to focus of this review.

CYTOREDUCTIVE NEPHRECTOMY

Local therapy in mRCC involves non-curative resection of the primary tumour. In a subset of patients with solitary metastases, a curative metastasectomy can be carried out. The rationale is largely based on tumour seeding and self-seeding principles.[4] Large prospective RCTs have shown a significant survival benefit of cytoreductive nephrectomy (CN) plus systemic therapy over systemic

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therapy alone (13,6 months *vs.* 7,8 months) in the IN-Fα-era.[5,6] However, such data are missing in the era of TT. Retrospective data based on large population-based studies consistently suggest a survival benefit for CN plus TT over TT alone but definitive conclusions cannot be made to date. Therefore, prognostic models have been created for clinical trial design and risk-directed therapy. There are two major risk classification systems. The MSKCC model links five pre-treatment features (Karnofsky performance status (PS), LDH levels, haemoglobin levels, serum calcium levels and time from diagnosis to system treatment) with survival in patients with mRCC treated in the immunotherapy-era (1992-2004), creating good, intermediate and high groups.[7] The second model is the IMDC risk stratification system, which has been derived from a retrospective, multicentre study from seven different oncology centres in North America. The criteria are applicable to patients with mRCC treated within the TT-era, including six factors (Karnofsky, PS, time from diagnosis to treatment, haemoglobin levels, serum calcium, neutrophilia, and thrombocytosis) to stratify patients in favourable, intermediate and poor prognosis groups.[8] The importance of adequate patient selection should be stressed as data suggest that patients with a life expectancy <12 months or at least four IMDC negative prognostic risk criteria (poor risk) may not benefit from cytoreductive surgery.[9] There are currently two large prospective trials ongoing, aiming to establish the role of CN in mRCC in the era of TT. The SURTIME trial showed no differences in progression free survival (PFS) comparing upfront CN plus adjuvant TKI therapy with deferred CN after four weeks TKI therapy. However, a trend was observed for improved overall survival (OS) in the deferred CN arm.[10] The Clinical Trial to Assess the Importance of Nephrectomy (CARMENA), a phase III intention-to-treat non-inferiority trial for CN plus sunitinib versus sunitinib-only recently reported non-inferiority for OS of sunitinib-only in MSKCC poor and intermediate risk patients who were in immediate need of TT.[11] These trials led to the adaptation of EAU guidelines on CN; refraining from cytoreduction in all poor risk patients and in intermediate risk patients who require immediate TT. However, delayed CN should still be discussed in intermediate risk patients with long-term TT response. Favourable risk patients, not immediately requiring TT, should still be offered cytoreductive surgery as data suggest improved survival and the delay of TT with potential debilitating toxicities.[12]

These paradigm-shifting studies highlight the importance of adequate patient selection for cytoreductive surgery. Future studies will further define prognostic factors identifying those patients, possibly underrepresented in the CARMENA population, who do benefit from CN.

SYSTEMIC TREATMENT OF MRCC

Since the development of a wide range of new therapeutic agents, systemic therapy beyond the traditional cytotoxic chemotherapeutics evolved to be the main stay therapy for mRCC.[10] In the last decade, the appearance of different forms of TT including immunotherapy, VEGF inhibitors and mTOR inhibitors with their emerging benefits, drastically changed the therapeutic landscape of mRCC and multiple agents are now tested in clinical trials. Initially, most first-line agents have been compared to placebo or IFN- α, but newer designed trials have a VEGFR-inhibitor (sunitinib or sorafenib) as control.

CHEMOTHERAPY

Unlike for other tumours, there is almost no room for cytotoxic chemotherapy in the treatment of mRCC. Data about the use of 5-fluorouracil in combination with immunotherapeutic agents like interferon-alpha (IFN-α) and interleukin-2 (IL-2) in the treatment of clear cell RCC (ccRCC) remain controversial and its use is not recommended in first-line.[10,11]

IMMUNOTHERAPY

The era of immunotherapy started with the use of IFN-α and IL-2.[12] Overall response was good (15–20%) with even 7–9% of the treated patients obtaining complete remission (CR).[12–14] Therefore, they were considered the backbone of systemic treatment in mRCC until 2005.

The use of **IFN-α** has been extensively investigated comparing it with both non-immunotherapy (like vinblastine or medroxyprogesterone) and IL-2 treatment. The initial trials showed a modest survival benefit and better remission compared to the control arms.[12,14] This benefit, however, was limited to specific subsets of patients with ccRCC and favourable MSKCC risk criteria.[7]

High-dose **IL-2** (HDIL-2) was approved by the FDA in 1992 based on data of phase II clinical trials.[15–17] As for IFN-α, complete and durable responses with HDIL-2 was only achieved in selected ccRCC cases with a good PS and lung metastases only. No biomarkers are available to predict durable responses and the high toxicity of this regimen has limited its use to only the fittest patients treated in experienced centres. With the rise of TT, several trials compared outcome of HDIL-2 with previous or subsequent TT in mRCC patients. The Proleukin Observational Study to Evaluate the Treatment Patterns and Clinical Response in Malignancy (PROCLAIM) registry is the largest observational clinical database in the US of patients with mRCC or metastatic melanoma, who were treated with HDIL-2 alone, in combination or sequenced with other treatments.[18,19] Their

first results suggest that patients treated with HDIL-2 with or without prior TT experienced prolonged clinical benefit and that it remains a valid option for eligible patients in both first line setting as well as after failure of prior TT.[19] In conclusion, the role of HDIL-2 in the treatment of mRCC patients remains limited to those with good PS and organ function in specialised treatment centers.[19,20] This is reflected in the EAU guidelines as well, where it is not recommended using IFN-α or IL-2 as monotherapeutic agent in a first-line treatment anymore.

IMMUNE CHECKPOINT BLOCKADE

Since RCC is an immunogenic tumour, several clinical trials with different immune checkpoint inhibitors are ongoing in both first- and second-line settings. The use of immunotherapy has known a revival thanks to the monoclonal antibody nivolumab (NIV), an **immune checkpoint inhibitor** targeting T-cell receptor Programmed Death ligand-1 (PD-1) to restore tumour specific T-cell immunity.[2,21] It was approved as second-line treatment for mRCC in 2015 based upon a phase III randomised controlled trial (RCT) (CheckMate 025) comparing NIV to everolimus in mRCC patients.[22] Next to better QoL and fewer grade 3-4 adverse events, medium OS (mOS) was superior in the NIV-arm (25 months *vs.* 19.6 months mOS) with a hazard ratio for death of 0.73 (98.5% CI, 0.57 to 0.93; P=0.002) in the advantage of NIV (NCT01668784).[22] Importantly, based on recent results of the CheckMate-214 trial, EAU recommendations for treatment of first-line mRCC will be updated. CheckMate-214 is a phase III trial testing two immune checkpoint inhibitors, NIV and ipilimumab (IPI) against sunitinib in treatment-naïve RCC. It showed superior response rates and OS in intermediate and poor risk patients treated with NIV + IPI and this combination is now recommended to offer as a first-line treatment in both intermediate and poor risk disease. Final results will define their role in the favourable disease group but recommendations concerning this group remain weak.[23] Several other clinical phase III trials with these immune checkpoint inhibitors alone or in combination therapy are ongoing in first and second line settings. The Javelin Renal 101 and KEYNOTE-426 trials evaluate sunitinib versus a combination of a checkpoint inhibitor (avolumab or pembrolizumab respectively) plus axitinib. In the first-line setting, lenvatinib in with everolimus or pembrolizumab versus sunitinib alone was tested (NCT02811861). These trials are expected to be terminated by 2020.

TARGETED THERAPY

Thanks to the improved understanding of the pathogenic mechanisms of RCC, which involve VHL mutations and aberrations in the PI3K/AKT/mTOR pathway, the treatment landscape of mRCC has changed dramatically during the past decade. This goes along with significant improvements in survival with prolongation of mOS up to 28 months.[19] After the approval of sorafenib and sunitinib the first two VEGFR-TKIs, several other targeted agents have been approved going from other VEGFR inhibitors (pazopanib, axitinib, cabozantinib, and lenvatinib), the VEGF monoclonal antibody bevacizumab and mTOR inhibitors (temsirolimus and everolimus).

TYROSINE KINASE INHIBITORS

Receptor tyrosine kinases, like vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), are important in the pathogenesis of clear-cell RCC through the key role of the von Hippel–Lindau (VHL) gene.[24,25] VHL is a tumour suppressor gene, involved in different hypoxia inducible proteins such as VEGF and PDGF and it is inactivated in up to 80% of the sporadic ccRCC cases VHL. Finally, this VHL inactivation results in a persistent stimulation of receptor tyrosine kinases and subsequent promotion of tumour angiogenesis, growth and metastasis.

Sorafenib (SOR) was the first VEGFR-TKIs to be approved for treatment of mRCC in 2005 based on the results of a phase III RCT comparing this multi-kinase inhibitor to placebo in patients with advanced RCC after first-line therapy failure.[26] In this trial oral SOR prolonged PFS (5.5 months) with a 56% reduction in risk of progression compared to placebo (2.8 months). To improve its efficacy, the combination of SOR with other TTs or immunotherapy has been tested in multiple trials.[26–29] It is now recommended as treatment option in second or third-line setting after failure of multiple VEGFR-TKIs.

The antitumor activity of **sunitinib** (SUN), a multi-targeted inhibitor of VEGFR, PDGFR and other receptor tyrosine kinases, was demonstrated in different phase II trials suggesting that SUN was a promising compound in the second-line treatment of mRCC, which resulted in its approval by the FDA as second-line treatment.[24,25,30] The efficacy of SUN in the first-line setting was tested in a phase III trial, comparing SUN with INF-α. For the first time in the TT-era, VEGFR-TKI treatment resulted in an improved prognosis in treatment-naïve mRCC patients with a prolonged OS (26.4 months) and PFS (11 months) compared to INF-α (21.8 months and 5 months, respectively) and an acceptable safety profile.[31] The data of this trial support the use of SUN in first-line treatment of mRCC in all MSKCC risk groups.

Pazopanib (PAZ), an oral angiogenesis inhibitor of VEGFR,

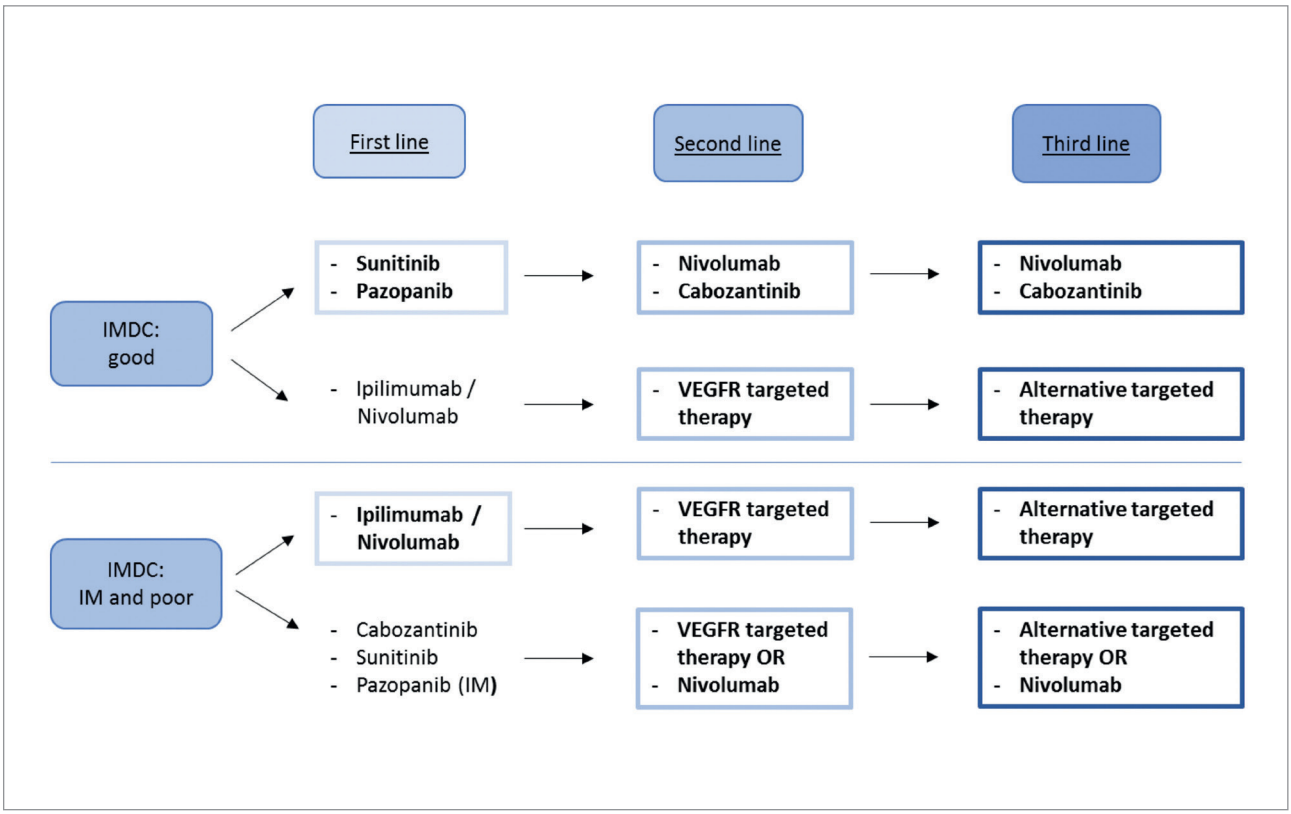

FIGURE 1. Updated EAU recommendations for systemic treatment in mRCC patients.

PDGFR and c-Kit, is also recommended as a first-line treatment for mRCC patients of all MSKCC risk groups based on trials comparing PAZ with placebo in patients with or without previous immunotherapy.[32] To compare efficacy and safety between PAZ and sun the COMPARZ trial and PISCES trial were designed, comparing a continuous dose of PAZ with SUN in six week cycles. PAZ-treatment appeared to be non-inferior to the intermittent treatment with SUN. However, the safety profile and QoL was significantly better in patients treated with PAZ in both trials.

To prevent off-target activities seen in the first-generation TKIs, **axitinib** was designed. It is a selective, second-generation inhibitor of VEGFR 1, 2 and 3 with a relative higher potency. It was first evaluated as a second-line treatment in the phase III AXIS trial, where it was compared with SOR.[33,34] Treatment with axitinib resulted in a significant prolonged PFS (6.7 months *vs.* 4.7 months, HR 0.67, 95% CI 0.544-0.812) and established axitinib as a second-line treatment option for mRCC patients. However, when compared to SOR in first-line setting, no improvement of PFS was observed.[35]

Cabozantinib (CAB) is designed to target the problem of resistance to other antiangiogenic drugs. It is a small-molecule tyrosine kinase inhibitor against VEGFR as well as MET and AXL, which are important in the pathobiology of mRCC. A single-arm open-label phase I trial showed anti-tumour activity and an acceptable safety profile, comparable to other TKIs.[36] Based on these promising results, the METEOR phase III trial enrolled mRCC patients who had progressed after one or more VEGFR-TTs, comparing CAB with everolimus. PFS was significantly longer in the CAB-arm compared with everolimus (7.4 months *vs.* 3.8 months), with a 42% lower rate of progression or death.[37] In their second interim analysis, CAB also resulted in an increased OS compared to everolimus (21.4 months *vs.* 16.5 months).[37] Therefore, CAB can be recommended in the treatment of mRCC patients, previously treated with one or more failed VEGFR-targeted therapies in all risk categories and irrespective of previous treatments.

Finally, **lenvatinib** was developed as a multi-target TKI with a very wide range of activity, targeting VEGFR1, VEGFR2, and VEGFR3 and with inhibitory activity against fibroblast growth factor receptors (FGFR1, FGFR2, FGFR3, and FGFR4), PDGFRα, RET and KIT. It has only been tested as a combination therapy with everolimus, showing superior results compared to lenvatinib or everolimus alone.[38]

BEVACIZUMAB, A MONOCLONAL ANTIBODY AGAINST VEGFR

The benefit and safety of the anti-VEGFR monoclonal an-

tibody **bevacizumab** (BEV) was demonstrated in different phase II clinical trials, as monotherapy or in combination with targeted agents.[39–41] Two phase III trials compared the safety and efficacy of the combination BEV plus INF- α to INF- α alone in treatment-naïve mRCC patients. The AVOREN trial showed that the combination resulted in a prolonged PFS (10.2 months *vs.* 5.4 months; HR 0.63, 95% CI 0.52-0.75).[42] In the open-label CALGB 90206 trial, the combination arm showed a better OS (18.3 months, 95% CI 16.5 to 22.5 months) compared to IFN-α alone (17.4 months, 95% CI 14.4 to 20 months) but failed to meet the predefined criteria for statistical significance.[43,44] However, the median PFS time were prolonged (8.5 months *vs.* 5.2 months) together with an increase in objective response rate (according to the RECIST criteria). For both studies, the toxicity was higher in the combination arm with more grade 3 and 4 adverse events but these data were as expected and in line with precious observations.[43,44] Based on these results, the combination of BEV with INF-α is established as first-line treatment in treatment-naïve patients with cc-mRCC and favourable-to-intermediate MSKCC risk scores.[42]

mTOR INHIBITORS

Disrupting mTOR-signalling suppresses cell cycle progression and angiogenesis. Since a dysregulation in the angiogenesis process is prominent in RCC, treatment with mTOR inhibitors, appeared to be clinically relevant.[45] **Temsirolimus** (TEM) is an inhibitor of mTOR, which is involved in regulation of cell growth and proliferation, preventing progression from the G1 to S phase of the cell cycle. It has been investigated in both pre- and post VEGFR-TKI settings. In a phase III RCT, newly diagnosed mRCC patients with a poor prognosis received TEM, IFN-α or a combination.[46] TEM alone resulted in a longer OS compared to INF-α (10.9 months *vs.* 7.3 months, respectively), where the combination of IFN-α with Tem only showed an increased toxicity without survival benefit (mOS of 8.4 months). The difference in OS in this phase III trial was the primary basis of the FDA approval in 2007 for TEM and the EAU guidelines now recommend offering Tem in first-line treatment of mRCC in patients with a poor prognosis.[47] However, since TT with newer agents like VEGFR-TKIs were approved, comparison with these agents instead of IFN-α became more and more interesting. The phase III INTORSECT trial compared the use and safety of TEM as a second-line treatment with SOR after disease progression in patients who received SUN but failed to show a PFS benefit in patients treated with TEM.[48] Therefore, TEM is not recommended in mRCC patients with disease progression after VEGFR-TKI treatment. Unlike TEM, **everolimus**, another mTOR-inhibitor, is recommended in patients with mRCC who progressed on VEGF-TKI therapy. It was approved by the FDA based on data from the RECORD I study, a phase III trial comparing everolimus with placebo in patients who progressed on (multiple) VEGF-TKI treatment(s).[49] Final analysis showed a significant benefit in PFS of 4.9 months in the everolimus group compared to 1.9 months in the placebo group, which is a 67% reduction in risk of progression for the everolimus group. Sub-analysis of patients progressed after only one previous VEGFR-TKI treatment had an even longer PFS of 5.4 months. The toxicity profile of everolimus was as expected for mTOR inhibitors but differs from the profile of VEGF-TKIs which can be an advantage for patients who show intolerance against TKI treatment. The RECORD-3 study was performed to determine the optimal sequence of TT comparing first-line everolimus followed by SUN with first-line SUN followed by everolimus in treatment-naïve mRCC patients.[50] After primary analysis, first-line treatment with everolimus did not show non-inferiority and the median PFS was shorter compared to SUN (7.9 months *vs.* 10.7 months, respectively; HR 1.4, 95% CI 1.2-1.8) thereby confirming the use of first-line SUN followed by everolimus at progression.[51]

SEQUENCING THERAPY IN mRCC

Multiple systemic therapies are available nowadays for the treatment of mRCC making its therapeutic landscape very complicated. Moreover, the most beneficial timing and sequence of these agents still has to be determined. It is very hard to predict the optimal treatment sequence, since not every possible combination is tested in clinical trials and direct comparison of different trials is not advised due to heterogeneity within the different study cohorts. Importantly, recommendations made by the EAU will be updated based on new data of the CheckMate-214 trial.[23]

In **first line therapy**, cytokine related therapies (INF-α or IL-2) are not recommended anymore but newer targeted therapeutic agents replace them. The EAU guidelines will recommend NIV + IPI as the standard of care in intermediate to poor risk disease but not in favourable risk group.[23] VEGFR-TKIs, like sunitinib, pazopanib and cabozantinib, remain in the first-line setting if treatment with NIV plus IPI is not safe or available or in favourable-risk disease according to the IMDC risk classification (*Figure 1*). Other agents such as BEV plus IFN-α (good- and intermediate-risk) and TEM (poor-risk disease) are all approved in the first-line setting but they are not widely used and evidence for these agents is less convincing. Therefore, the EAU guidelines do not favour these therapeutic agents. Several trials have established the efficacy of SOR, PAZ and axitinib as **sec-**

KEY MESSAGES FOR CLINICAL PRACTICE

1. Targeted therapy has replaced cytokine related therapies like IFN-α and HDIL-2.
2. The IMDC risk criteria stratify patients into in favourable, intermediate and poor prognosis groups in the era of targeted therapy.
3. Do not perform cytoreductive surgery in poor risk patients, discuss deferred surgery in intermediate risk patients with long term TT response and offer CN in all good risk patients, not requiring immediate systemic therapy.
4. The combination of nivolumab plus ipilimumab has replaced VEGFR-TKIs in treatment-naïve mRCC patients with intermediate- and poor-risk disease. Sunitinib and pazopanib remain the treatment of choice in the favourable-risk group as first line treatment.
5. Recommendations concerning second- and third line treatments remain weak. VEGFR-TKIs should be preferred in patients that are nivolumab-refractory. In patients treated with upfront nivolumab, sunitinib or pazopanib are recommended in second-line therapy.
6. No patient characteristics or biomarkers have been described useful in determining the best treatment sequence.

ond-line therapy after cytokine treatment, with axitinib showing superior results compared to SOR in this setting. With the rise of TT, the question which treatment should be recommended in case of disease progression after one or more lines of VEGFR-TKI became important. Based on the results of the RECORD-I study everolimus was recommended as second-line therapy following VEGFR-TKI. However, nivolumab and cabozantinib both showed superiority compared to everolimus in the CheckMate 025 and METEOR trial respectively. Therefore, NIV or CAB are recommended as second-line therapeutic agents after failure of first-line VEGFR-TT and everolimus should be considered only if other agents are not safe or tolerable.[52] It should be recommended to use both drugs in sequence as a second and third line treatment after VEGFR-TKI failure. Due to the heterogeneity of the study cohorts comparison between these three treatments cannot be made. Concerning **third-line treatment** strong recommendation are currently lacking. According to the EAU guidelines, NIV and CAB remain first choice after failure of multiple lines of VEGFR therapy, whereas SOR is recommended after VEGFR- and mTOR-TT. If the patient is not yet treated with CAB or NIV, these should be preferred in all IMDC risk groups, however evidence in these settings is low. Inhibition of multiple pathways with **combination therapy** offers a theoretical benefit of both overcoming resistance and the possibility of therapeutic synergy but recommendations are missing since no combination has proven to be better than single-agent therapy and persistent issues of intolerability. One exception is the combination of lenvatinib plus everolimus, tested in a phase II trial comparing patients receiving everolimus, lenvatinib or the combination showing significant prolongation of PFS in the combination arm compared to everolimus alone (14.6 months *vs.* 5.5 months, HR 0.40, 95% CI 0.24-0.68) but no difference was observed when compared with lenvatinib alone[38]. This combination now has regulatory approval and is an alternative in the VEGFR-refractory disease despite the fact that only phase II data are available.

CONCLUSION

In the past decennia, the therapeutic landscape of mRCC drastically changed. However, most of the new agents (VEGFR-TKIs and mTOR inhibitors) have failed to translate into a significant survival benefit and firm recommendations by the EAU guidelines on the best sequence for TT are still lacking. Due to its complexity, decisions concerning treatment of mRCC require a multidisciplinary approach incorporating both surgical resection and systemic therapy. Future goals in the treatment of mRCC should be to better select patients benefitting these therapeutic agents. With multiple first- and second-line options already available nowadays, optimal treatment selection will probably include genome sequencing and predictive

biomarker development aimed at identifying specific patient subgroups in whom long term treatment response could be achieved.

REFERENCES

1. Ferlay J, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. Eur J Cancer. 2013;49:1374–403.

2. Choueiri TK, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015;373:1914–823.

3. Ljungberg B, et al. The epidemiology of renal cell carcinoma. Eur Urol. 2011;60:615–21.

4. Comen E, et al. Clinical implications of cancer self-seeding. Nat Rev Clin Oncol. 2011;8:369–77.

5. Flanigan R, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med. 2001;345:1655–9.

6. Mickisch GH, et al. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: A randomised trial. Lancet. 2001;358:966–70.

7. Motzer RJ, et al. Prognostic factors for survival of patients with stage IV renal cell carcinoma: memorial sloan-kettering cancer center experience. Clin Cancer Res. 2004;10:6302S.

8. Heng DY, et al. Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. Eur Urol. 2014;66:704–10.

9. Bex A, et al. Immediate versus deferred cytoreductive nephrectomy (CN) in patients with synchronous metastatic renal cell carcinoma (mRCC) receiving sunitinib (EORTC 30073 SURTIME). Present. 2017 ESMO Congress. Madrid, Spain, Abstract LBA35.

10. Appleman LJ, et al. Systemic therapy following metastasectomy for renal cell carcinoma: Using insights from other clinical settings to address unanswered questions. Urol Oncol Semin Orig Investig. 2018;36:17–22.

11. Gore ME, 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: 641–8.

12. Coppin C, et al. Immunotherapy for advanced renal cell cancer. Cochrane Database Syst Rev. 2005;1:CD001425.

13. Fisher RI, et al. Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. Cancer J Sci Am. 2000;6, Suppl 1: S55-57.

14. Medical Research Council Renal Cancer Collaborators. Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomised controlled trial. Lancet. 1999;353(9146):14-7.

15. Alva A, et al. Contemporary experience with high-dose interleukin-2 therapy and impact on survival in patients with metastatic melanoma and metastatic renal cell carcinoma. Cancer Immunol Immunother. 2016;65:1533–44.

16. Rosenberg SA, et al. Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2: Identification of the antigens mediating response. Ann Surg. 1998;228:307–19.

17. Yang JC, et al. Randomised study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. J Clin Oncol. 2003;21:3127–32.

18. Curti B, et al. Improved survival and tumour control with Interleukin-2 is associated with the development of immune-related adverse events: Data from the PROCLAIM registry. J Immunother. 2017;Cancer 5:1–9.

19. Clark JI, et al. Impact of Sequencing Targeted Therapies With High-dose Interleukin-2 Immunotherapy: An Analysis of Outcome and Survival of Patients With Metastatic Renal Cell Carcinoma From an On-going Observational IL-2 Clinical Trial: PROCLAIMSM. Clin Genitourin Cancer. 2017;15:31–41.e4.

20. Gill DM et al. Overview of Current and Future First-Line Systemic Therapy for Metastatic Clear Cell Renal Cell Carcinoma. Curr Treat Options Oncol. 2018;19:6.

21. Ribas A, et al. Immunotherapy Directed at PD-1. N Engl J Med. 2012;26:2517–9.

22. Escudier B, et al. CheckMate 025 Randomised Phase 3 Study: Outcomes by Key Baseline Factors and Prior Therapy for Nivolumab Versus Everolimus in Advanced Renal Cell Carcinoma [Figure presented]. Eur Urol. 2017;72:962–71.

23. Powles T, et al. Updated European Association of Urology Guidelines Recommendations for the Treatment of First-line Metastatic Clear Cell Renal Cancer. Eur Urol. 2017;3:9–13.

24. Motzer RJ, et al. Sunitinib in Patients With Metastatic Renal Cell Carcinoma. Jama. 2006;295:2516.

25. Robert J, et al. Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma. N Engl J Med. 2007;356:115–24.

26. Escudier B, et al. Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma. N Engl J Med. 2007;356:125–34.

27. Eichelberg C, et al. SWITCH: A randomised, sequential, open-label study to evaluate the efficacy and safety of sorafenib-sunitinib versus sunitinib-sorafenib in the treatment of metastatic renal cell cancer. Eur Urol. 2015;68:837–47.

28. Procopio G, et al. Sorafenib with interleukin-2 vs sorafenib alone in metastatic renal cell carcinoma: The ROSORC trial. Br J Cancer. 2011;104:1256–61.

29. Procopio G, et al. Overall survival for sorafenib plus interleukin-2 compared with sorafenib alone in metastatic renal cell carcinoma (mRCC): Final results of the ROSORC trial. Ann Oncol. 2013;24:2967–71.

30. Motzer RJ, et al. Sunitinib Efficacy Against Advanced Renal Cell Carcinoma. J Urol 2007;178:1883–7.

31. Motzer RJ, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009;27:3584–90.

32. Sternberg CN, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomised phase III trial. J Clin Oncol. 2010;28:1061–8.

33. Rini BI, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): A randomised phase 3 trial. Lancet. 2011;378:1931–9.

34. Motzer RJ, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: Overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol. 2013;14:552–62.

35. Hutson TE, 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;14:1287–94.

36. Choueiri TK, et al. A phase I study of cabozantinib (XL184) in patients with

renal cell cancer. Ann Oncol. 2014;25:1603–8.

37. Choueiri TK, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2016;17:917–27.

38. Motzer RJ, 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.

39. Unverzagt S, et al. Immunotherapy for metastatic renal cell carcinoma. Cochrane Database Syst Rev. 2017;5:CD011673.

40. Yang JC, et al. A Randomised Trial of Bevacizumab, an Anti–Vascular Endothelial Growth Factor Antibody, for Metastatic Renal Cancer. N Engl J Med. 2003;349:427–34.

41. Négrier 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;12:673–80.

42. Escudier B, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet. 2007;370:2103–11.

43. Rini BI, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol. 2008;26:5422–8.

44. Rini BI, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: Final results of CALGB 90206. J Clin Oncol. 2010;28:2137–43.

45. Larkin JM, et al. Kinase inhibitors in the treatment of renal cell carcinoma. Crit Rev Oncol Hematol. 2006;60:216–26.

46. Hudes G, et al. Temsirolimus, interferon alfa, or both for advanced renal cell carcinoma. N Engl J Med. 2007;356:2271–81.

47. Kwitkowski VE, et al. FDA Approval Summary: Temsirolimus as Treatment for Advanced Renal Cell Carcinoma. Oncologist. 2010;15:428–35.

48. Hutson TE, et al. Randomised phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2014;32:760–7.

49. Motzer RJ, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. Cancer. 2010;116:4256–65.

50. Knox JJ, et al. Final overall survival analysis for the phase II RECORD-3 study of first-line everolimus followed by sunitinib versus first-line sunitinib followed by everolimus in metastatic RCC. Ann Oncol. 2017;28:1339–45.

51. Motzer RJ, et al. Phase II randomised trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. J Clin Oncol. 2014;32:2765–72.

52. Powles T, et al. Updated EAU Guidelines for Clear Cell Renal Cancer Patients Who Fail VEGF Targeted Therapy. Eur Urol. 2016;69:4–6.