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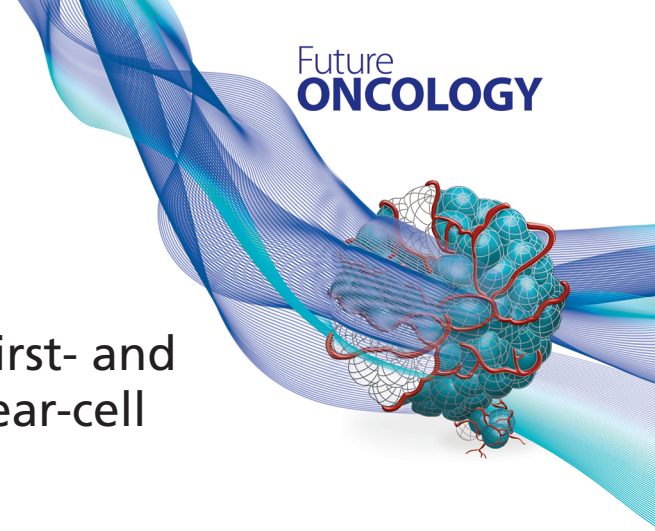

Consensus paper: current state of first- and second-line therapy in advanced clear-cell renal cell carcinoma

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The therapy of advanced (clear-cell) renal cell carcinoma (RCC) has recently experienced tremendous changes. Several new treatments have been developed, with PD-1 immune-checkpoint inhibition being the backbone of therapy. Diverse immunotherapy combinations change current first-line standards. These changes also require new approaches in subsequent lines of therapy. In an expert panel, we discussed the new treatment options and how they change clinical practice. While first-line immunotherapies introduce a new level of response rates, data on second-line therapies remains poor. This scenario poses a challenge for clinicians as guideline recommendations are based on historical patient cohorts and agents may lack the appropriate label for their in guidelines recommended use. Here, we summarize relevant clinical data and consider appropriate treatment strategies.

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Renal cell carcinoma (RCC) is a common type of cancer: it accounts for 2–3% of all cancers [1]. About 80% of all kidney cancers are renal cell carcinomas (RCC) [2]. The highest incidence worldwide can be found in the western world [1]. In addition to the many therapeutic options provided over the last years, new treatments for advanced RCC have been developed with PD-1 immune-checkpoint inhibition being the backbone of therapy. Based on recently published data, dual checkpoint blockade with nivolumab and ipilimumab has been approved for the first-line treatment of adult patients with intermediate-/poor-risk advanced RCC. The European Medicine Agency (EMA) furthermore approved the tyrosine kinase inhibitor (TKI) axitinib in combination with either pembrolizumab or avelumab for treating advanced RCC independently of the risk group [3,4]. These changes require new approaches in subsequent lines of therapy. While the low level of evidence is a hurdle in clinical practice, the limitation of the

Table 1. Models for risk assessment in advanced renal cell carcinoma.

Risk factor	IMDC [8,9]	MKSCC [6,7]
Karnofsky performance status <80%	✓	✓
Time from diagnosis to treatment <1 year	✓	✓
Hemoglobin concentration <LLN	✓	✓
Calcium concentration >ULN (IDMC)	✓	
Corrected calcium >10 mg/dl (MSKCC)		✓
Neutrophil count >ULN	✓	
Platelet count >ULN	✓	
LDH concentration >1.5x ULN		✓
Evaluation	**IMDC [8,9]**	**MKSCC [6,7]**
Favorable-risk group	0 risk factors	0 risk factors
Intermediate-risk group	1–2 risk factors	1–2 risk factors
Poor-risk group	≥3 risk factors	≥3 risk factors

IDMC International Metastatic RCC Database Consortium,: LLN: Lower limit of normal; MSKCC: Memorial Sloan Kettering Cancer Center; ULN: Upper limit of normal.

label may restrict the use of certain agents in subsequent therapeutic lines. Today, prospective studies in patients in whom checkpoint inhibitor therapy has failed remain scarce and jeopardize strong recommendations.

In an expert panel, the core panel (PJG, MOG, VG and PI) prepared the discussion on these new data and how it may translate into current treatment strategies of advanced clear-cell RCC (ccRCC) in daily clinical practice. The following content is based on that discussion including our own experience. We will introduce the recommendations issued by European medical societies of interest, such as the guidelines of the European Association of Urology (EAU) and the European Society for Medical Oncology (ESMO). We refer to those guidelines for different reasons, for example, their timely provision and their flexibility. The EAU guidelines on RCC is being updated every year, a further update has been published as the approval of the combination of pembrolizumab and axitinib became apparent [1,3]. The ESMO guidelines were updated in 2019 and take into account the approvals of the combination of nivolumab and ipilimumab, as well as of tivozanib as first-line treatments [2]. We also include the German S3 guideline with the Association of the Scientific Medical Societies in Germany, the German Cancer Society and the German Cancer Aid as editors and the German Society for Urology (DGU) and the German Society of Hematology and Medical Oncology (DGHO) as the leading medical societies [5]. The expert panel is well aware of the different levels of evidence and the different inherent approached these guidelines use as part of their consenting process.

First-line therapy of advanced ccRCC

Risk assessment

Two models are used to assess the risk or prognosis of patients with advanced or metastatic (cc)RCC. The Memorial Sloan Kettering Cancer Center (MSKCC) risk score [6,7] was the first one to report its prognostic value in metastatic RCC (mRCC). While it has been developed in patients either receiving chemotherapy or cytokine therapy, the score was meanwhile validated in cohorts with targeted therapies, particularly TKIs. The International Metastatic RCC Database Consortium (IMDC) reassessed the value of established factors and added additional parameters and thereby improved its predictability [8,9]. The major advantage of the IMDC scoring system is its improved accuracy in identifying patients with higher risk, compared with the MSKCC system. The risk factors covered by each of the models and their rating can be found in Table 1. Of note, a single risk factor already results in the allocation of the patient to the intermediate prognosis group, with the clinical implication of having the choice between nivolumab and ipilimumab versus axitinib and either one of the checkpoint inhibitors avelumab or pembrolizumab.

Recommendation

We recommend evaluating each patient's risk/prognosis by using the IMDC score before selecting first-line treatment.

Unaddressed topics

However, there are unanswered questions. Is clinical risk assessment still relevant with the new treatment options at hand – especially with regard to the fact that these prognostic scores were not validated using checkpoint

inhibitors? In addition, factors such as brain metastases, tumor burden outside the kidney and poor risk according to IMDC will have to be taken into consideration when choosing systemic therapies [10]. Is the combination of the PD-1 inhibitor nivolumab and the anti-CTLA-4 inhibitor ipilimumab only an option for intermediate-/poor-risk ccRCC? Obviously, novel reliable biomarkers are needed, but candidates remain scarce. In our opinion, the discrimination of favorable- or intermediate-/poor-risk patients is more important than ever, especially when taking into account the label of the combination of nivolumab and ipilimumab. However, do we need to differentiate between intermediate or poor risk at all? Currently, the recommendations for the treatment are the same for both groups. The results of the CheckMate-214 trial evaluating nivolumab plus ipilimumab confirmed this strategy. No difference between intermediate- or poor-risk patients in the immunotherapy arm could be seen regarding overall response rate (ORR), progression-free survival (PFS) or overall survival (OS) [11]. Finally, yet importantly: do we even need a risk assessment, now that the combination of axitinib plus either pembrolizumab or avelumab has been approved for treating all risk groups?

First-line treatment options

Currently, several treatment options are available for first-line therapy. They include different substance classes such as inhibitors of the mammalian target of rapamycin (mTOR) and VEGFR and checkpoint inhibitors. VEGFR-TKIs approved for first-line treatment of advanced (cc)RCC include sunitinib, pazopanib, tivozanib and cabozantinib. However, it has to be of note that tivozanib is not available in some countries such as the USA. Except for cabozantinib, which is indicated for treating intermediate- and poor-risk advanced (cc)RCC, there is no restriction for VEGFR-TKI use based on risk groups according to the label, although the majority of these patients were intermediate- or favorable-risk patients. Different trials evaluated the efficacy and safety of sunitinib (1034, COMPARZ) [12–14], pazopanib (VEG105192, COMPARZ) [14–16], tivozanib (TIVO-1) [17], axitinib [18,19] and cabozantinib (CABOSUN) [20,21]. Furthermore, studies compared sunitinib and pazopanib (e.g., COMPARZ [14]). The mTOR inhibitor temsirolimus has been investigated in poor-risk patients [22], and the VEGF inhibitor bevacizumab was assessed in different trials (AVOREN [23,24], BEVLIN [25], CALGB 90206 [26,27]). The combination of the checkpoint inhibitors nivolumab plus ipilimumab is approved for treating intermediate- and poor-risk (cc)RCC (CheckMate [CM]-214) [28–30]. The most recent options for the treatment of all risk groups are the combinations of pembrolizumab plus axitinib (Keynote [KN]-426 [31,32]) and avelumab plus axitinib (JAVELIN Renal 101 trial [33,34]). Atezolizumab plus bevacizumab were evaluated in the IMmotion151 trial [35–37]. We summarized the most important results of the relevant clinical studies in Table 2.

Recommended first-line treatment strategies issued by ESMO, EAU, SITC, DGU & DGHO

As interpretation of the data may ultimately be translated into guidelines, it becomes necessary to point out that there are marked differences among those guidelines. The causes may relate to the composition of the guideline panel, the methodology, the society which provides the guidelines and their specific background or environment (i.e., for example, with regard to reflecting a different healthcare system). Thus, the authors felt it to be relevant to at least refer to some of the guidelines that are most commonly used.

ESMO guidelines [2] (level of evidence, grade of recommendation):

- Favorable-risk advanced ccRCC:
  - Recommended: pembrolizumab plus axitinib (I,A), avelumab and axitinib(II,B);
  - Alternatives*: sunitinib (I,A), pazopanib (I,A) or tivozanib (II,B).
- Intermediate-risk advanced ccRCC:
  - Recommended: pembrolizumab plus axitinib (I,A), nivolumabplus ipilimumab (I,A) or avelumab and axitinib (II,B);
  - Alternatives*: sunitinib (I,A), pazopanib (I,A), cabozantinib (II,B).
- Poor-risk advanced ccRCC:
  - Recommended: pembrolizumab plus axitinib (I,A), nivolumab plusipilimumab (I,A) or avelumab and axitinib (II,B);

Table 2. First-line treatment of advanced/metastatic ccRCC – summarized data.

Substances	Patients	PFS (median)	OS (median)	ORR	Adverse events	Ref.
Approved therapies						
Sunitinib (n = 375) vs **IFN-α** (n = 375) **Phase III**	Untreated, metastatic clear-cell RCC, all-risk groups (MSKCC), ECOG PS 0-1	11 vs 5 months (HR: 0.54; 95% CI:: 0.45–0.64; p < 0.001)	26.4 vs 21.8 months (HR: 0.821; 95%: CI: 0.673–1.001; p = 0.051 unstratified log-rank test; HR: 0818, 95%: CI: 0.669–0.999; p = 0.049 stratified log-rank test)	47 vs 12% (p < 0.001) CR: n = 11 vs n = 4)	Sunitinib group: All grades: diarrhea (61%), fatigue (54%), nausea (52%), dysgeusia (46%) Grade 3: hypertension (12%), fatigue (11%), diarrhea (9%), hand-foot syndrome (9%)	[12,13]
VEG105192 *total population*: **pazopanib** (n = 290) vs **placebo** (n = 145) *treatment-naive population*: **pazopanib** (n = 155) vs **placebo** (n = 78) **Phase III**	Untreated or one prior cytokine-based systemic therapy, advanced or metastatic clear-cell RCC, predominantly favorable and intermediate-risk groups (MSKCC), ECOG PS 0-1	Total population: 9.2 vs 4.2 months (HR: 0.46; 95% CI: 0.34–0.62; p < 0.0001) Treatment-naive population: 11.1 vs 2.8 months (HR: 0.40; 95% CI: 0.27–0.60; p < 0.0001)	Total population: 22.9 vs 20.5 months (HR: 0.91; 95% CI: 0.71–1.16; p = 0.224) Treatment-naive population: 22.9 vs 23.5 months (HR: 1.01; 95% CI: 0.72–1.42)	Total population: 30 vs 3% CR: <1% vs.0% Treatment-naive population: 32 vs 4% CR: not specified	Pazopanib group: All grades: ALT increase (53%), AST increase (53%), diarrhea (52%), hyperglycemia (43%), hypertension (40%) grade 3/4: 45%	[15,16]
COMPARZ **pazopanib** (n = 557) vs **sunitinib** (n = 553) **Phase III**	Untreated advanced or metastatic clear-cell RCC, all-risk groups (MSKCC and IMDC), ECOG PS 0-1	8.4 vs 9.5 months (HR: 1.05; 95% CI: 0.90–1.22)	28.4 vs 29.3 months (HR: 0.91; 95% CI: 0.76–1.08; p = 0.28)	31 vs 25% (p = 0.03) CR: n = 1 vs n = 3	Pazopanib: All grades: increased AST (61%), increased ALT (60%), fatigue (55%), leukopenia (43%), thrombocytopenia (41%), lymphocytopenia (38%), neutropenia (37%), hypophosphatemia (36%), increased total bilirubin (36%), hypoalbuminemia (33%), increased creatinine (32%), anemia (31%), changes in hair color (30%) grade 3/4: increased ALT (15%), increased AST (11%), fatigue (11%), hand-foot syndrome (6%) Sunitinib: All grades: leukopenia (78%), thrombocytopenia (78%), neutropenia (68%), fatigue (63%), anemia (60%), increased AST (60%), lymphocytopenia (55%), hypophosphatemia (52%), hand-foot syndrome (50%), increased creatinine (46%), increased ALT (43%), hypoalbuminemia (42%), dysgeusia (36%) Grade 3/4: thrombocytopenia (22%), neutropenia (20%), fatigue (18%), lymphocytopenia (15%), hand-foot syndrome (12%), hypophosphatemia (9%), anemia (7%), leukopenia (6%) Sunitinib: higher risk of hematologic laboratory abnormalities of any grade and grade 3/4 Pazopanib: higher risk of ALT or bilirubin increases of any grade and of ALT and AST of grade 3/4	[14]

In bold: study name; comparator; study type.
CR: Complete response; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IDMC: International Metastatic RCC Database Consortium; MSKCC: Memorial Sloan Kettering Cancer Center; PS: Performance Status; RCC: Renal cell carcinoma.

Table 2. First-line treatment of advanced/metastatic ccRCC – summarized data (cont.).

Substances	Patients	PFS (median)	OS (median)	ORR	Adverse events	Ref.
CABOSUN **cabozantinib** (n = 79) vs **sunitinib** (n = 78) **Phase II**	Untreated advanced or metastatic clear-cell RCC, intermediate- or poor-risk groups (IMDC), ECOG PS 0-1	8.6 vs 5.3 months (HR: 0.48; 95% CI: 0.31–0.74; p = 0.0008)	26.6 vs 21.2 months (HR: 0.80; 95%-CI: 0.53–1.21)	20 vs 9% CR: 0 vs 0%	Cabozantinib vs sunitinib: All grades: 92 vs 89% Grade 3/4: 68 vs 65% Cabozantib: All grades: diarrhea (73%), hypertension (66%), fatigue (64%), AST increase (60%), ALT increase (55%), decreased appetite (49%), hand-foot syndrome (43%), dysgeusia (41%) grade 3/4: hypertension (28%), diarrhea (10%), hand-foot syndrome (8%) Sunitinib: All grades: fatigue (68%), platelet count decreased (61%), diarrhea (54%), anemia (46%), hypertension (44%) grade 3/4: hypertension (19%), fatigue (17%), diarrhea (11%), platelet count decreased (8%)	[20,21]
Total population: **tivozanib** (n = 260) vs **sorafenib** (n = 257) *Treatment-naive population*: **tivozanib** (n = 181) vs **sorafenib** (n = 181) **Phase III**	Untreated or one prior systemic therapy, advanced or metastatic clear-cell RCC, predominantly favorable and intermediate-risk groups (MSKCC), ECOG PS 0-1	Total population: 11.9 vs 9.1 months (HR: 0.797; 95% CI: 0.639–0.993; p < 0.042) Treatment-naive population: 12.7 vs 9.1 months (HR: 0.756; 95% CI: 0.580–0.985; p < 0.037)	Total population: 28.8 vs 29.3 months (HR: 1.245; 95% CI:: 0.954–1.624; p = 0.105)	Total population: 33.1 vs 23.3% (p = 0.014) CR: 1.2 vs 0.8%	Tivozanib group: All grades: proteinuria (72%), hypertension (44%), increased lipase (46%), low hemoglobin (41%), increased amylase (40%) Grade 3/4: hypertension (27%), increased lipase (11%), fatigue (5%), increased amylase (5%) Sorafenib group: All grades: proteinuria (73%), hypophosphatemia (71%), increased lipase (64%), hand-foot syndrome (54%), increased amylase (53%), increased AST 51%, low hemoglobin (49%) Grade 3/4: hypophosphatemia (26%), increased lipase (24%), hypertension (19%), and-foot syndrome (17%)	[17]
Temsirolimus + IFN-α (n = 210) vs **temsirolimus** (n = 209) vs **IFN-α** (n = 207) **Phase III**	Untreated advanced (stage IV or recurrent disease) RCC (predominantly clear-cell), intermediate- or poor-risk group (MSKCC), Karnofsky PS ≥60%	Temsirolimus vs IFN-α: 5.5 vs 3.1 monthsTemsirolimus + IFN-α vs IFN-α: 4.7 vs 3.1 months	Temsirolimus vs IFN-α: 10.9 vs 7.3 months (HR: 0.73; 95% CI: 0.58–0.92; p = 0.008) Temsirolimus + IFN-α vs IFN-α: 8.4 vs 7.3 months (HR: 0.96; 95% CI:: 0.76–1.20; p = 0.70)	Temsirolimus + IFN-α vs temsirolimus vs IFN-α: 8.1 vs 8.6 vs 4.8% CR: not specified	Temsirolimus + IFN-α: All grades: asthenia (62%), anemia (61%), fever (60%), nausea (40%) Grade 3/4: anemia (38%), asthenia (28%), neutropenia (15%) Temsirolimus: All grades: asthenia (51%), rash (47%), anemia (45%) Grade 3/4: anemia (20%), asthenia (11%), hyperglycemia (11%) IFN-α: All grades: asthenia (64%), fever (50%), anorexia (44%), anemia (42%), nausea (41%) Grade 3/4: asthenia (26%), anemia (22%), neutropenia (7%)	[22]
AVOREN **bevacizumab + IFN-α** (n = 327) vs **placebo + IFN-α** (n = 322) **Phase III**	Untreated, metastatic clear-cell RCC, all risk groups (MSKCC), but predominantly favorable and intermediate risk, Karnofsky PS ≥70%	10.2 vs 5.4 months (HR: 0.63; 95% CI: 0.52–0.75; p = 0.0001)	23.3 vs 21.3 months (unstratified HR: 0.91; 95% CI: 0.76–1.10; p = 0.336; stratified HR: 0.86; 95% CI, 0.72–1.04; p = 0.1291)	31 vs 13% (p = 0.0001) CR: 1 vs 2%	Bevacizumab + IFN-α: All grades: pyrexia (45%), anorexia (36%), fatigue (33%), bleeding (33%) Grade 3/4: fatigue (12%), asthenia (10%), proteinuria (7%)	[23,24]

In bold: study name; comparator; study type.
CR: Complete response; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IDMC: International Metastatic RCC Database Consortium; MSKCC: Memorial Sloan Kettering Cancer Center; PS: Performance Status; RCC: Renal cell carcinoma.

Table 2. First-line treatment of advanced/metastatic ccRCC – summarized data (cont.).

Substances	Patients	PFS (median)	OS (median)	ORR	Adverse events	Ref.
BEVLiN **bevacizumab + IFN-α** (n = 146) **Phase II**	Untreated, metastatic clear-cell RCC, favorable- and intermediate-risk group (MSKCC), Karnofsky PS ≥70% or ECOG PS 0-2	15.3 months	30.7 months	28.8% CR: 2.2%	All grades: 84.2% ≥grade 3: 42.5%	[25]
CALGB 90206 **bevacizumab + IFN-α** (n = 369) vs **IFN-α** (n = 363) **Phase III**	Untreated, metastatic clear-cell RCC, all risk groups (MSKCC), Karnofsky PS ≥70%	8.5 vs 5.2 months ($p < 0.0001$)	OS: 18.3 vs 17.4 months (unstratified log-rank p = 0.097; HR: 0.86; 95% CI: 0.73–1.01; stratified log-rank p = 0.069)	25.5 vs 13.1% ($p < 0.0001$) CR: not specified	≥grade 3: 79 vs 61% ($p < 0.0001$) Bevacizumab + IFN-α: All grades: fatigue (93%), anorexia (71%), proteinuria (71%), nausea (58%), neutropenia (43%) ≥grade 3: fatigue (37%), anorexia (17%), proteinuria (15%), hypertension (11%)	[26,27]
CheckMate 214 *intermediate- and high-risk population:* **nivolumab + ipilimumab** (n = 425) vs **sunitinib** (n = 422) *Total population*: **nivolumab + ipilimumab** (n = 550) vs **sunitinib** (n = 546) **Phase III**	Untreated, advanced clear-cell RCC, all risk groups (IMDC), Karnofsky PS ≥70%	Intermediate- and high-risk population: 8.2 months vs 8.3 months (HR: 0.77; 95% CI 0.65–0.90; p = 0.0014) Total population: 9.7 vs 9.7 months (HR: 0.85, 95% CI: 0,73–0,98, p = 0.027)	Intermediate- and high-risk population: not reached vs 26.6 months (HR 0.66, 95% CI 0.54–0.80, $p < 0.0001$) Total population: not reached vs 37.9 months (HR 0.71; 95% CI: 0.59–0.86, p = 0.0003)	Intermediate- and high-risk population: 42 vs 29% (p = 0.0001) Total population: 41 vs 34% (p = 0.015)	Nivolumab + ipilimumab: grade 3/4: increased lipase (10%), increased amylase (6%), increased ALT (5%) 8 treatment-related deaths Sunitinib: grade 3/4: hypertension (17%), fatigue (10%), hand-foot syndrome (9%) 4 treatment-related deaths	[28–30]
KEYNOTE-426 **pembrolizumab + axitinib** (n = 432) vs **sunitinib** (n = 429) **Phase III**	Untreated, advanced (stage IV) clear-cell RCC, all risk groups (IMDC)	15.1 vs 11.1 months (HR 0.69; 95% CI 0.57–0.84; $p < 0.001$)	Not reached vs not reached (HR 0.53; 95% CI: 0.38–0.74; $p < 0.0001$)	59.3 vs 35.7% ($p < 0.001$) CR: 5.8 vs 1.9%	All grades: 98.4 vs. 99.5% ≥grade 3: 75.8 vs 70.6% Pembrolizumab + axitinib: All grades: diarrhea (54.3%), hypertension (44.5%), fatigue (38.5%), hypothyroidism (35.4%) ≥grade 3: hypertension (22.1%), ALT increased (13.3%), diarrhea (9.1%), AST increased (7%) Sunitinib: All grades: hypertension (45.4%), diarrhea (44.9%), hand-foot syndrome (40%), fatigue (37.9%), hypothyroidism (31.5%), nausea (31.5%), dysgeusia (30.8%) ≥grade 3: hypertension (19.3%), platelet count decreased (7.3%), neutrophil count decreased (6.8%), fatigue (6.6%), neutropenia (6.6%)	[31,32]

In bold: study name; comparator; study type.
CR: Complete response; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IDMC: International Metastatic RCC Database Consortium; MSKCC: Memorial Sloan Kettering Cancer Center; PS: Performance Status; RCC: Renal cell carcinoma.

Table 2. First-line treatment of advanced/metastatic ccRCC – summarized data (cont.).

Substances	Patients	PFS (median)	OS (median)	ORR	Adverse events	Ref.
JAVELIN Renal 101 *PD-L1-positive (≥1% IC) population*: **avelumab + axitinib** (n = 270) vs **sunitinib** (n = 290) *total population*: **avelumab + axitinib** (n = 442) vs **sunitinib** (n = 444) **Phase III**	Untreated, advanced (stage IV) clear-cell RCC, all risk groups (MSKCC, IMDC), ECOG PS 0-1	PD-L1-positive population: 13.8 vs 7.2 months (HR: 0.61; 95% CI: 0.47–0.79; p < 0.001) Total population: 13.8 vs 8.4 months (HR: 0.69; 95% CI: 0.59–0.84; p < 0.001)	PD-L1-positive population: deaths from any cause in 13.7% (median follow-up 11.6 months) vs 15.2% (median follow-up 10.7 months) (HR: 0.82; 95%.CI: 0.53–1.28; p = 0,38) Total population: deaths from any cause in 14.3% (median follow-up 12 months) vs 16.9% (median follow-up 11.5 months) (HR: 0.78; 95%.CI: 0.55–1.08; p = 0.14)	PD-L1-positive population: 55.2 vs 25.5% CR: 4.4 vs 2.1% Total population: 51.4 vs 25.7% CR:3.4 vs 1.8%	All grades: 99.5 vs 99.3% ≥grade 3: 71.2 vs 71.5% Avelumab + axitinib: all grades: diarrhea (62.2%), hypertension (49.5%), fatigue (41.4%), nausea (34.1%), hand-foot syndrome (33.4%), dysphonia (30.6%) ≥grade 3: hypertension (25.6%), diarrhea (6.7%), ALT increased (6%), hand-foot syndrome (5.8%) Sunitinib: All grades: diarrhea (47.6%), fatigue (40.1%), nausea (39.2%), hypertension (36.0%), hand-foot syndrome (33.7%), dysgeusia (32.3%) ≥grade 3: hypertension (17.1%), anemia (8.2%), neutropenia (8%), thrombocytopenia (6.2%), neutrophil count decreased (5.7%), platelet count decreased (5%)	[33,34]
Unapproved therapies						
IMmotion151 *PD-L1-positive (≥1% IC) population*: **atezolizumab + bevacizumab** (n = 178) vs **sunitinib** (n = 184) *Total population*: **atezolizumab + bevacizumab** (n = 454) vs **sunitinib** (n = 461) **Phase III**	Untreated, advanced predominantly clear-cell (sarcomatoid) RCC, all risk groups (MSKCC)	PD-L1-positive population: 11.2 vs 7.7 months (HR: 0.74; 95% CI: 0.57–0.96; p = 0.0217) Total population: 11.2 vs 8.4 months (HR: 0.83; 95% CI: 0.70–0.97)	PD-L1-positive population: 34.0 vs 32.7 months (HR: 0.84; 95%.CI: 0.62–1.15) *Total population:* 33.6 vs 34.9 months (HR: 0.93; 95% CI: 0.76–1.14)	PD-L1-positive population: 43 vs.35% CR: 9 vs 4% Total population: 37 vs 33% CR: 8 vs 2%	All grades: 91 vs 96% Grade 3/4: 40 vs 54%	[35–37]
Axitinib (n = 192) vs **sorafenib** (n = 96) **Phase III**	Untreated, metastatic clear-cell RCC, all risk groups (predominantly favorable and intermediate risk, MSKCC), ECOG PS 0-1	10.1 vs 6.5 months (HR: 0.77; 95% CI: 0.56–1.05; p = 0.038)	21.1 vs 23.3 months (HR: 0.995; 95% CI: 0.731–1.356; p = 0.4883)	32 vs 15% (p = 0.0006) CR: 0 vs 0%	Axitinib: All grades: diarrhea (50%), hypertension (49%), weight decrease (37%), fatigue (33%) Grade 3/4: hypertension (14%), diarrhea (9%), asthenia (8%), weight decrease (8%), hand-foot syndrome (7%) Sorafenib: All grades: diarrhea (40%), hand-foot syndrome (39%), fatigue (26%) Grade 3/4: hand-foot syndrome (16%), diarrhea (5%), asthenia (5%) Significantly more common with axitinib than with sorafenib (all grades): Diarrhea (50%), hypertension (49%), weight decrease (37%), decreased appetite (29%), dysphonia (23%), hypothyroidism (21%), upper abdominal pain (16%) Significantly more common with sorafenib than with axitinib (all grades): Hand-foot syndrome (39%), rash (20%), alopecia (19%), erythema (19%)	[18,19]

In bold: study name; comparator; study type.
CR: Complete response; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IDMC: International Metastatic RCC Database Consortium; MSKCC: Memorial Sloan Kettering Cancer Center; PS: Performance Status; RCC: Renal cell carcinoma.

- Alternatives*: sunitinib (I,A), pazopanib (I,A), cabozantinib (II,B).

*where recommended treatment not available or contra-indicated.

EAU guidelines [3] (level of evidence, strengths of recommendation):

- Risk assessment by the IMDC model;
- Favorable-risk advanced ccRCC:
  - Standard: pembrolizumab plus axitinib (1b, strong);
  - Alternatives: sunitinib (1b, strong) or pazopanib (1b, strong), if patients cannot receive a checkpoint inhibitor.
- Intermediate- or poor-risk advanced ccRCC:
  - Standard: either pembrolizumab plus axitinib (1b, strong) or nivolumab plus ipilimumab (1b, strong);
  - Alternatives: cabozantinib (2a, strong), sunitinib (1b, strong), or pazopanib (1b, strong), if patients cannot receive a checkpoint inhibitor.

German S3 guidelines ([5] (level of evidence, strengths of recommendation):

- Risk assessment by the IMDC model
- Advanced ccRCC – all risk groups:
  - Pembrolizumab plus axitinib (1-,A), avelumab plus axitinib (1-,B);
  - Alternatives – good-risk advanced ccRCC (alphabetical order): bevacizumab plus IFN-a, pazopanib, sunitinib, or tivozanib (1++,A).
- Intermediate- or poor-risk advanced ccRCC:
  - Pembrolizumab plus axitinib, nivolumab plus ipilimumab (1-,A) or avelumab plus axitinib (1-,B);
  - Alternatives: cabozantinib, pazopanib, sunitinib,or tivozanib (1-,B) or bevacizumab plus IFN-a (1-,0);
  - Alternatives poor-risk (weak recommendation): temsirolimus, pazopanib (1+,0).

SITC guidelines [10]:

- Risk assessment by the IMDC model;
- Favorable-risk advanced ccRCC:
  - Recommended: pembrolizumab plus axitinib;
  - Other options: nivolumab plus ipilimumab, sunitinib, HD IL-2, Anti-VEGF TKI, Anti-PD-1 monotherapy.
- Intermediate- or poor-risk advanced ccRCC:
  - Recommended: either nivolumab plus ipilimumab or pembrolizumab plus axitinib;
  - Other options: Anti-PD-1 monotherapy.

Summary

Until recently, the standard treatments for advanced ccRCC independent of risk group were the TKIs pazopanib and sunitinib. As both TKIs have comparable efficacy, the decision to use either drug has depended on preference and safety profile [14]. This approach was supported by the results of the PISCES trial [38]. Differences in outcome measures have been heavily debated, as both TKIs exert a similar adverse event (AE) profile, which offers differences in incidence and severity of single AEs rather than an entirely distinct safety profile.

The role of tivozanib is less clear. Tivozanib may have similar efficacy to pazopanib and sunitinib, but no head-to-head comparison exists. Clinical trial data suggest that tivozanib may increase PFS as compared with sorafenib, but was inferior in OS [17]. In addition, tivozanib may have a better tolerability profile than pazopanib or sunitinib, but again, absence of direct comparative data weakens this point of differentiation. Cabozantinib use in the first line

is restricted to intermediate- or poor-risk patients. The results of the CABOSUN trial revealed that cabozantinib was more efficacious regarding progression-free survival (PFS) than the comparator sunitinib [20,21], while it did not show any significant overall survival (OS) improvement. However, OS was a secondary end point in this Phase II trial, and the statistical analysis was underpowered. The tolerability of cabozantinib appeared comparable to sunitinib in this pivotal trial, but required frequent treatment interruptions and dose-reductions. However, overall, side effects appeared manageable. In clinical routine, cabozantinib treatment is often offered at a lower dose (40 mg once daily instead of 60 mg once daily) and is being escalated, once tolerability is established.

Other treatment options such as temsirolimus or bevacizumab plus IFN-α have become less important in clinical practice. Temsirolimus is only suitable for high-risk patients, but has shown an overall survival benefit compared with cytokine treatment [22]. The combination of bevacizumab plus IFN-α was shown to have improved efficacy compared with cytokine treatment, however, its safety profile is dominated by cytokine-based adverse events. This combination is an option for patients, if TKI therapy-related intolerable toxicities such as hand-foot syndrome or diarrhea prevail, as well as in patients with low compliance.

More recently, the role of checkpoint inhibitors in first-line therapy – at least for the intermediate- and poor-risk groups – was shown in the CM-214 trial, which compared nivolumab plus ipilimumab to sunitinib [28–30]. The combination showed better efficacy with regards to response rate and OS for the aforementioned groups, but not for the good-risk group while it offered a favorable safety profile and better health-related quality of life. Nevertheless, long-term or even permanent administration of corticosteroids was necessary in 29% of patients, indicating higher risks of relevant immune-associated adverse events [28,30].

The KN-426 trial compared pembrolizumab plus axitinib to sunitinib [31,32,39]. Again, the results showed an OS benefit for this combination. In addition, PFS and objective response rate (ORR) (60.2%) were improved, which led to a low rate of primary treatment failure (11.3%). The rate of adverse events was slightly higher for the combination, in particular regarding hypertension, (grade 3/4) diarrhea and hepatitis.

Similarly, the JAVELIN Renal 101 trial demonstrated a better efficacy for the combination of avelumab plus axitinib versus sunitinib regarding PFS and ORR (51%), with a comparable if not slightly better safety profile (indirect comparison) [33,34]. However, significance for OS benefit has not been reported yet, as data is immature.

The combination of atezolizumab plus bevacizumab did not show any survival benefit compared with sunitinib in the IMmotion151 trial, while PFS was extended in the primary efficacy population of PD-L1-positive patients [35–37]. Therefore, the application to change the European marketing authorization for atezolizumab to treat advanced ccRCC was not pursued [40].

Recommendations

The combination of pembrolizumab plus axitinib may be the future standard to treat favorable-risk advanced disease. The significance of avelumab plus axitinib in this risk group has not yet finally defined due to immature OS data. Given the low adverse event rate in this patient population and their differences in clinical outcome between trials, additional follow-up is required. The variability of results is underlined by the updated OS analysis in the KN 426 trial with a hazard ratio (HR) for OS of 1.06 for this subgroup [39,41]. Besides the uncertainty of the magnitude of treatment effect, the use of these combinations exposes patients to additional toxicities. Other options, e.g. if the use of pembrolizumab or avelumab is contraindicated, are pazopanib, sunitinib, or presumably tivozanib. There may also be a small but relevant proportion of patients, which could be followed by active surveillance. Elderly patients or patients with good risk and low tumor burden disease may also be considered for TKI monotherapy. In addition, the respective safety profiles may influence the decision between pazopanib, sunitinib or tivozanib.

We either recommend the combination of pembrolizumab plus axitinib or the combination of nivolumab plus ipilimumab to treat intermediate- or poor-risk advanced ccRCC. Axitinib plus avelumab may be another option, yet, the combination has not shown a significant survival benefit. The decision between these combinations may be guided by the safety profile. It seems that the combination of nivolumab and ipilimumab is the more tolerable one, given the lower rate of grade 3/4 AEs and its benefit versus sunitinib with regards to health-related quality of life measures. However, it causes more immune-related adverse events than the combination of either avelumab or pembrolizumab and axitinib (see section “Biomarker – immunotherapies”). Contraindications for the use of ipilimumab, nivolumab, avelumab or pembrolizumab are corticosteroid therapy, post transplantation, autoimmune diseases, patient preference for oral application (also for logistical reasons), and deficient compliance (depends on individual conditions). For these patients, the alternative treatment option is cabozantinib (intermediate- and

poor-risk patients), sunitinib, pazopanib or presumably tivozanib (no clear recommendation for specific risk groups for the last three substances).

Unaddressed topics

Do possible differences between PD-1 antibodies such as pembrolizumab and PD-L1 antibodies such as avelumab exist? Is it wise – also in view of the already approved combinations – to replace a monotherapy (with TKIs) by a combination therapy? Are other options – namely TKIs – only reasonable, if contraindications for the combination therapy exist? Moreover, shall we use checkpoint inhibitors based on PD-L1 expression levels? We need more research and clinical trials to address these topics and to find conclusive answers.

Positive HIV, HBV or HCV tests were exclusion criteria in the CM-214 and in the KN-426 studies. However, there is evidence that checkpoint inhibitors might be effective and do not show any new safety signals in HIV-positive patients with advanced cancers [42,43]. The same might be true for patients with chronic hepatitis B or C infections [44,45]. Patients with autoimmune diseases were also excluded from the CM-214, KN-426 and JAVELIN Renal 101 trials. Results of a systematic review – including 123 patients with cancer and autoimmune diseases receiving checkpoint inhibitors – showed that the use of checkpoint inhibitors was followed by exacerbations of pre-existing autoimmune diseases and increasing numbers of immune-related (ir)AEs in 75% of patients [46]. Exacerbations of autoimmune diseases as well as irAEs were manageable with steroids in most cases, other immunosuppressive treatments were necessary in some cases (16%). Three patients died due to AEs. Overall, the evidence for using checkpoint inhibitors in patients with chronic infections, autoimmune diseases, or cancer is still low and needs further evaluation.

Biomarker – immunotherapies

Which biomarker should we use to decide on immunotherapies? Up to now, the most widely evaluated marker is PD-L1. However, we have to bear in mind, that the investigators of the relevant clinical trials used different PD-L1 tests. These tests can differ in their sensitivity and can have either positive or negative results, depending on the population. In the CM-214 trial, patients with PD-L1-positive tumors had the highest benefit of the treatment with nivolumab and ipilimumab seemingly selecting for patients with a higher rate of complete remissions [28]. Nevertheless, PD-L1 expression did not correlate with survival benefit in either the JAVELIN Renal 101 or in the KN-426 trial [34,47]. The current follow-up in these trials does not allow drawing any conclusions on the potential role of PD-L1 as a biomarker for complete remission in checkpoint inhibitor and TKI combinations.

There is increasing data that suggests that molecular signatures may be more important than the PD-L1 status. At the ASCO annual meeting 2019 Choueiri *et al.* presented a biomarker analysis of the JAVELIN-101 Renal study [48]. This analysis focused on CD8 expression, gene expression profiling (26-gene JAVELIN Renal 101 signature), mutations and polymorphisms. The results demonstrated an association of higher numbers of CD8-positive cells with longer PFS in the combination arm and with shorter PFS in the sunitinib arm. In addition, an elevated expression of the genes comprised in the JAVELIN Renal 101 signature correlated with PFS in the combination arm. In addition, mutations in certain genes were connected with PFS in both arms [48].

Another example is provided with the IMmotion151 trial by Rini *et al.* who evaluated angiogenesis and T-effector gene expression signatures [49]. They showed that the combination of atezolizumab plus bevacizumab improved PFS versus sunitinib in T-effector^{High} and angiogenesis^{Low} tumors. In contrast, sunitinib improved PFS in patients with an angiogenesis^{High} gene signature versus an angiogenesis^{Low}. Another finding was that the favorable-risk group could be characterized by a predominant angiogenesis^{High} gene signature.

In addition, it could well be that also Next-Generation Sequencing may play a more relevant role in the management of mRCC in the future as molecular profiling helps us to decipher the complex orchestration of molecular alterations during progression of metastatic spread.

Recommendations, unaddressed topics

It appears that PD-L1 expression may be a factor to guide the decision to either use a combination of two checkpoint inhibitors or a combination of checkpoint inhibitor and TKI. Shall we base our treatment choice on PD-L1 expression and risk group? Is it feasible to treat PD-L1-positve advanced ccRCC of intermediate or poor risk with nivolumab and ipilimumab and, in contrast, to treat PD-L1 negative advanced ccRCC with a checkpoint inhibitor and TKI? One advantage of the treatment with nivolumab plus ipilimumab is the long follow-up of the CM-214 trial (32 months) [30]. The follow-up of the KN-426 trial evaluating pembrolizumab plus axitinib is

shorter (12 months [31] and 19 months [41]). Besides, the combination of nivolumab plus ipilimumab is associated with long-term responses. There was a high rate of complete responses (CR) (11%) of which the majority were of a prolonged duration (88%). The rate of CRs was highest in the subgroup of patients with PD-L1-positive tumors (16%). In the JAVELIN Renal 101 trial, treatment with avelumab plus axitinib resulted in a similar median PFS in the PD-L1-positive subgroup and in the total population [33,34]. Therefore, it seems, that in this trial the PD-L1 status did not influence PFS. On the other hand, there were more patients with primarily progressive disease compared with pembrolizumab plus axitinib in the KN-426 trial, indicating a broader level of activity for the TKI-checkpoint inhibitor combinations [30,31]. Bearing in mind that cross-trial comparison introduces bias and head-to-head data is currently missing, the HR for OS was best for pembrolizumab plus axitinib (0.53 [31]), while the HR for nivolumab plus ipilimumab was 0.66 [30]. Interestingly, the OS benefit of the combination avelumab plus axitinib was less pronounced (HR 0.82 [33]) while other efficacy parameters were comparable to those of the combination pembrolizumab plus axitinib (HRs for PFS: avelumab plus axitinib 0.74 [33]; pembrolizumab plus axitinib 0.69 [31,32]). Selection and potential differences in healthcare systems may account for variable efficacy and safety outcomes, irrespective of the differences in medications used. Overall, nivolumab plus ipilimumab seem to be associated with a clinically meaningful chance for long-term response or even potential long-term benefit in patients with PD-L1-positive mRCC. Pembrolizumab plus axitinib may be a good choice for patients with a high tumor burden or imminent complications upon further progression. Further follow-up will help to understand how differences in efficacy and safety may guide treatment choice in the clinic. Another topic of interest is that various tests exist for the assessment of PD-L1 expression. Not all of these are available in Europe. However, so far, testing of PD-L1 expression is not necessary according to the European labels for nivolumab, ipilimumab, avelumab or pembrolizumab. The lack of marker-driven treatment decisions underlines the need for objective and reliable biomarkers.

Second-line therapy of advanced ccRCC

The new first-line standards in advanced ccRCC put our current second-line options out of date. Until recently, second-line recommendations followed the high level of evidence for sequential therapies with TKIs (first-line TKI followed by a second-line TKI). While first-line immunotherapies introduce a new level of activity, data on second-line therapies after these remain poor. This scenario poses a challenge for clinicians as guideline recommendations are based on historical patient cohorts and agents may lack an appropriate label for their in guidelines recommended use.

Second-line treatment options

In Table 3 we summarized important results of relevant trials in which different single agents or combinations were evaluated in second-line therapy [50–54]. Data for TKIs after failure of immunotherapies in second [55–60] or later lines [61–66] remains scarce (Table 3). Even recent randomized controlled studies only included a minority of patients after combinations of immunotherapies in first line [67]. Ongoing efforts are focusing to gain data on the sequence of second-line options after immune-oncology (IO)-mono or combination therapies. With the combination of TKI-IO in first-line, the picture becomes even more complex and prospective evaluation in a randomized fashion may become very difficult. The lack of Phase II trials in this context may also compromise the level of evidence presented in guidelines.

The recent published data from the PROCLAIM database demonstrated that HD IL-2 treatment yields durable responses among mRCC patients of all risk categories eligible for HD IL-2 therapy [69]. Especially the prolonged survival benefit in the favorable- and intermediate-risk groups supports the value of this option. However, in Germany it is rarely used. In addition to the promising HIF1-alpha blockade [70], emerging strategies include small molecule therapies that target IDO1, glutaminase, CXCR4 and TG2 [71].

Recommended second-line treatment strategies issued by ESMO, EAU, SITC, DGU & DGHO

ESMO guidelines [2] (level of evidence, grade of recommendation):

- Prior immunotherapy:
    - Standard: none;
    - Options: any TKI (IV, C), or lenvatinib + everolimus (IV, C).

Table 3. Second-line treatment and sequence immunotherapy → targeted therapy – summarized data.

Substances	Patients	PFS (median)	OS (median)	ORR	Adverse events	Ref.
AXIS **axitinib** (n = 361) vs **sorafenib** (n = 362) Phase III	Pretreated metastatic clear-cell RCC, all risk groups (MSKCC, IMDC), ECOG PS 0-1, one previous systemic first-line treatment with sunitinib, bevacizumab plus IFN-α, temsirolimus or cytokine	6.7 vs 4.7 months (HR: 0.665; 95% CI: 0.544–0.81; $p < 0.0001$)	20.1 vs 19.2 months (HR: 0.97; 95% CI: 0.80–1.17; n.s.)	19 vs 9% ($p = 0.0001$) CR: 0 vs 0%	Axitinib: All grades: creatinine elevation (55%), diarrhea (55%), hypertension (40%), fatigue (39%), hypocalcaemia (39%), anemia (35%), decreased appetite (34%), lymphopenia (33%), nausea (32%), dysphonia (31%) ≥grade 3: hypertension (16%), diarrhea (11%), fatigue (11%) Sorafenib: All grades: hypocalcaemia (59%), diarrhea (53%), anemia (52%), hand-foot syndrome (51%), hypophosphataemia (50%), lipase elevation (46%), creatinine elevation (41%) ≥grade 3: hand-foot syndrome (16%), hypophosphataemia (16%), lipase elevation (15%), hypertension (11%)	[50]
METEOR ***cabozantinib*** (n = 330) vs ***everolimus*** (n = 328) **Phase III**	Pretreated metastatic clear-cell RCC, all risk groups, at least one previous VEGFR-TKI	7.4 vs 3.9 months (HR: 0.51; 95% CI: 0.41–0.62; $p < 0.0001$)	21.4 vs 16.5 months (HR: 0.66; 95%.CI: 0.53–0.83; $p = 0.00026$)	17 vs 3% ($p < 0.0001$) CR: 0 vs 0%	Grade 1/2: 21 vs 32% Grade 3: 63 vs 52% Grade 4: 8 vs 8% Cabozantinib: Grade 3/4: hypertension (15%), diarrhea (13%), fatigue (11%) Everolimus: Grade 3/4: anemia (17%)	[51]
lenvatinib + everolimus (n = 51) vs **lenvatinib** (n = 52) vs **everolimus** (n = 50) **Phase II**	Advanced or metastatic, clear-cell RCC, pretreated with a VEGF-targeted therapy	Lenvatinib plus everolimus vs everolimus: 14.6 vs 5.5 months (HR: 0.40; 95% CI: 0.24–0.68; $p = 0.0005$) Lenvatinib plus everolimus vs lenvatinib: 14.6 vs 7.4 months (HR: 0.66; 95% CI: 0.30–1.10; $p = 0.12$) Lenvatinib vs everolimus: 7.4 vs 5.5 months (HR: 0.61; 95% CI: 0.38–0.98; $p = 0.048$)			Grade 3/4: everolimus (50%), lenvatinib (79%), lenvatinib + everolimus (71%) Lenvatinib + everolimus: Grade 3/4: diarrhea (20%) Lenvatinib: Grade 3/4: proteinuria (19%) Everolimus: Grade 3/4: anemia (12%)	[54]
RECORD-1 ***everolimus*** (n = 272) vs **placebo** (n = 138) **Phase III**	Metastatic clear-cell RCC, pretreated with sunitinib and/or sorafenib (bevacizumab, IL-2, or IFN-α also permitted), all risk groups (MSKCC)	4.0 vs 1.9 months (HR: 0.30; 95% CI: 0.22–0.40; $p < 0.0001$)	Not reached vs 8.8 months (HR: 0.83; 95% CI: 0.50–1.37; $p = 0.23$)	1 vs 0% CR: 0 vs 0%	Everolimus: All grades: anemia (91%), hypercholesterolemia (76%), hypertriglyceridemia (71%), hyperglycemia (50%), raised creatinine (46%), lymphopenia (42%), stomatitis (40%) Grade 3/4: lymphopenia (14%), hyperglycemia (12%), anemia (9%)	[52]

In bold: study name; comparator; study type.
CR: Complete response; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IDMC: International Metastatic RCC Database Consortium; MSKCC: Memorial Sloan Kettering Cancer Center; PS: Performance Status; RCC: Renal cell carcinoma.

Table 3. Second-line treatment and sequence immunotherapy → targeted therapy – summarized data (cont.).

Substances	Patients	PFS (median)	OS (median)	ORR	Adverse events	Ref.
CheckMate 025 ***nivolumab*** (n = 410) vs ***everolimus*** (n = 411) **Phase III**	Metastatic clear-cell RCC, pretreated with one or two regimens of antiangiogenic therapy, all risk groups (MSKCC), ECOG PS 0-1	4.6 vs 4.4 months (HR: 0.88; 95% CI: 0.75–1.03; p = 0.11)	25 vs 19.6 months (HR 0.73; 98.5% CI 0.57–0.93; p = 0.002)	25 vs 5% (OR: 5.98; 95% CI: 3.68–9.72; p < 0.001) CR: 1 vs <1%	All grades: 79 vs 88% Grade 3/4: 19 vs 37% Nivolumab: all grades: fatigue (33%) Everolimus: all grades: fatigue (34%), stomatitis (29%), anemia (24%), decreased appetite (21%), diarrhea (21%), rash (20%)	[53]
Sequence immunotherapy → targeted therapy						
Second-line treatment with **pazopanib, sunitinib, axitinib** and **cabozantinib** **Retrospective** trial (n = 70)	Metastatic clear-cell RCC, pretreated with checkpoint inhibitors, all risk groups (IMDC)	13.2 months		41.2%		[55]
VEGFR TKI (i.e., axitinib, cabozantinib, sunitinib) (n = 156) vs **mTOR inhibitors** (n = 28) *second line* VEGFR TKI (n = 44) vs mTOR inhibitors (n = 0) *third line* VEGFR TKI (n = 72) vs mTOR inhibitors (n = 20) *≥fourth line* VEGFR TKI (n = 40) vs mTOR inhibitors (n = 8) **data from 7 International mRCC Database Consortium (IMDC) centers**	Metastatic clear-cell RCC, pretreated with checkpoint inhibitors	Median time to treatment discontinuation (TTD) all lines: 5.3 vs 2.5 months (adjusted HR: 0.44, p = 0.002) second line: 3.8 months (TKI) third line: 5.7 vs 2.3 months ≥fourth line: 6.1 v. 3.2 months		*All lines:* 17 vs 5% second line: 23% (TKI) third line: 22 vs 6% ≥fourth line: 10 vs 0%		[56]
Second - to fourth-line treatment (n = 33), (**axitinib** n = 16, **pazopanib** n = 9, **sunitinib** n = 4, **cabozantinib** n = 4) **retrospective** analysis	Metastatic clear-cell RCC, pretreated with checkpoint inhibitors (front line), all risk groups (IMDC)	All patients (n = 28): 6.4 months axitinib (n = 14): 6.4 months pazopanib (n = 7): 5.6 months cabozantinib (n = 3): not reached sunitinib (n = 4): 2.9 months		*All patients* (n = 28): 29% axitinib: (n = 14): 29% pazopanib: (n = 7): 43% cabozantinib: (n = 3): 33% sunitinib: (n = 4): 0%	Grade 2-4 during first subsequent TKI: diarrhea (21%), fatigue (21%), mucositis (21%)	[57]
CheckMate 214 trial: patients with **subsequent TKI therapy** (n = 33)	Metastatic RCC, pretreated with nivolumab + ipilimumab	All patients: 8 months first-generation TKI (pazopanib/sunitinib): 8 months Second-generation TKI (axitinib/cabozantinib: 7 months	OS rate: 54% at 12 months	36%	≥grade 3: 42%	[58]

In bold: study name; comparator; study type.
CR: Complete response; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IDMC: International Metastatic RCC Database Consortium; MSKCC: Memorial Sloan Kettering Cancer Center; PS: Performance Status; RCC: Renal cell carcinoma.

Table 3. Second-line treatment and sequence immunotherapy → targeted therapy – summarized data (cont.).

Substances	Patients	PFS (median)	OS (median)	ORR	Adverse events	Ref.
Patients who had progressed on checkpoint-inhibitor treatment **cabozantinib** (n = 69)	Metastatic clear-cell RCC, pretreated with checkpoint inhibitors, all risk groups (IMDC)	Median time to treatment failure (TTF): 6.6 months	OS rate at 12 months: 53%	Partial response (best response): 33%		[59]
Axitinib (n = 40) **Phase II**	Metastatic clear-cell RCC, pretreated with checkpoint inhibitors, all risk groups (IMDC)	8.8 months		45% CR: 3%	All grades: fatigue (83%), hypertension (75%), hand-foot syndrome (64%), diarrhea (63%), decreased appetite (61%), dysphonia (55%), nausea/vomiting (50%), constipation (48%), hypothyroidism (43%), elevated creatinine (43%) Grade 3: hypertension (60%), dehydration (10%), fatigue (8%), hand-foot syndrome (8%) Grade 4: elevated lipase (3%)	[60]
METEOR **cabozantinib** (n = 18) vs **everolimus** (n = 14) Sub-analysis	Metastatic clear-cell RCC, all risk groups, at least one previous VEGFR TKI, cabozantinib treatment in third line after second-line nivolumab	Not reached vs 4.1 months (HR: 0.22, 95% CI: 0.07–0.65)	Not reached vs 16.3 months (HR: 0.56; 95% CI: 0.21–1.52)		Grade 3/4: 83 vs 64% Cabozantinib: Grade 3/4: fatigue (28%), hypertension (22%), hand-foot syndrome (17%), anemia (11%), asthenia (11%), diarrhea (11%) Everolimus: Grade 3/4: anemia (14%), fatigue (14%), hand-foot syndrome (7%)	[62]
TIVO-3 **tivozanib** (n = 175) vs **sorafenib** (n = 175) third- and fourth-line treatment **Phase III**	Metastatic clear-cell RCC, all risk groups (IMDC), two or three previous systemic therapies	All patients: 5.6 vs 3.9 months (HR: 0.73, 95% CI: 0.56–0.94; p = 0.016) Patients with previous checkpoint-inhibitor treatment: 7.3 vs 5.1 months (HR: 0.55, 95% CI 0.32–0.94; p = 0.016)	All patients: 16.4 vs 19.4 months (HR: 0.99, 95% CI: 0.76–1.29, p = 0.95)	All patients: 18 vs 8% (p = 0.017)	Tivozanib: All grades: hypertension (47%), diarrhea (35%), fatigue (33%), decreased appetite (28%), asthenia (26%), dysphonia (24%), stomatitis (20%) Grade 3 (no grade-4 event): hypertension (20%), asthenia (5%) Sorafenib: All grades: diarrhea (58%), hand-foot syndrome (46%), hypertension (28%), rash (26%), decreased appetite (25%), alopecia (22%), fatigue (21%), asthenia (20%), Grade 3/4: hypertension (14%), diarrhea (10%), hand-foot syndrome (10%), rash (8%), fatigue (5%)	[67]
Axitinib (n = 25), **cabozantinib** (n = 18), **other treatments** (n = 13) **Retrospective** analysis	Metastatic nonclear-cell and clear-cell RCC, all risk groups (IMDC), prior treatment included checkpoint inhibitors	All patients: median time to treatment failure (TTF): 9.4 months (all patients) Axitinib: median TTF: 9.7 months Cabozantinib: median TTF: not reached Other: median TTF: 7.1 months	All patients: 17.5 months Axitinib: 17.5 months Cabozantinib: not reached Other: 12.3 months	All patients: 30% Axitinib: 37% Cabozantinib: 41% Other: 0%		[63]

In bold: study name; comparator; study type.
CR: Complete response; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IDMC: International Metastatic RCC Database Consortium; MSKCC: Memorial Sloan Kettering Cancer Center; PS: Performance Status; RCC: Renal cell carcinoma.

Table 3. Second-line treatment and sequence immunotherapy → targeted therapy – summarized data (cont.).

Substances	Patients	PFS (median)	OS (median)	ORR	Adverse events	Ref.
Cabozantinib (n = 96) subgroup > third line (n = 20 with prior checkpoint-inhibitor therapy) **Italian Managed Access Program**	Metastatic RCC, all-risk groups (IMDC), progression after one or more prior systemic treatment, focus on prior checkpoint-inhibitor therapy	8 months	Not reached	36%	All patients (n = 96) Grade 3/4: 36%	[64]
Cabozantinib (n = 128, mainly within an expanded access program), pretreatment with immunotherapy (n = 37) **Retrospective** analysis	Pretreated metastatic nonclear-cell and clear-cell RCC, all-risk groups (IMDC), ECOG PS 0-2	All patients: 7.7 months *pretreatment with checkpoint inhibitors*: 12.0 months	All patients: 9.1 months *Pretreatment with checkpoint inhibitors* not reached	All patients: 26% *Pretreatment with checkpoint inhibitors* 30%	All patients: All grades: any (91%), asthenia (63%), mucositis (38%), diarrhea (36%), nausea/vomiting (25%) Grade 3/4: any (37%), asthenia (11%), diarrhea (9%), mucositis (5%)	[65]
Targeted therapy after checkpoint-inhibitor treatment (n = 102) second line: sunitinib (n = 23), pazopanib (n = 2), cabozantinib (n = 2) third line: axitinib (n = 24), cabozantinib (n = 23), everolimus (n = 10), sunitinib (n = 4), tivozanib (n = 2), sorafenib (n = 1), temsirolimus (n = 1) Fourth line: cabozantinib (n = 3), axitinib (n = 2), everolimus (n = 2), sunitinib (n = 1), pazopanib (n = 1), tiozanib (n = 1) **Canadian Kidney Cancer Information System**	Metastatic nonclear-cell and clear-cell RCC, all risk groups (IMDC), prior treatment with checkpoint inhibitors	Median TTF third-line axitinib vs third-line cabozantinib: 8.7 vs 6.2 months (HR: 0.77; 95% CI: 0.134–1.76; p = 0.53)	Third-line axitinib vs third-line cabozantinib: 19.7 vs 10.3 months (HR 0.77; 95% CI: 0.33–1.76; p = 0.79)			[61]
Lenvatinib alone (n = 10) or **in combination with everolimus** (n = 30) as at least second-line therapy Single-institution **retrospective** review.	Metastatic nonclear-cell and clear-cell RCC, all-risk groups (IMDC), prior treatment with checkpoint inhibitors	5.0 months	10.8 months	30%	Grade 3/4 fatigue (10%), diarrhea (10%), proteinuria (17.5%)	[74]

In bold: study name; comparator; study type.
CR: Complete response; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IDMC: International Metastatic RCC Database Consortium; MSKCC: Memorial Sloan Kettering Cancer Center; PS: Performance Status; RCC: Renal cell carcinoma.

- Prior TKI:
  - Standard: nivolumab (I, A), or cabozantinib (I, A);
  - Options: axitinib (II, B), everolimus (II, B), or lenvatinib + everolimus (II, B).

EAU guidelines [3] (level of evidence, strengths of recommendation):

- Prior immunotherapy:
  - Any VEGF targeted therapy that has not been used previously in combination with immunotherapy (4, weak).
- Prior TKI:
  - Nivolumab (1b), or cabozantinib (1b);
  - Alternative: axitinib (2b).

German S3 guideline [5] (level of evidence, strengths of recommendation):

- Prior VEGF/R inhibitor:
  - Standard: nivolumab, or cabozantinib (1–, A) or lenvatinib + everolimus (1–, B);
  - Alternatives: any other TKI (1+, 0).
- Prior immunotherapy:
  - No standard (expert consensus).
- Prior ipilimumab plus nivolumab:
  - Any other TKI-based therapy.
- Prior pembrolizumab plus axitinib or avelumab plus axitinib:
  - Any other TKI-based therapy.
- Prior mTOR inhibitor:
  - No standard (expert consensus);
  - Alternatives: TKI or nivolumab (2, B).

SITC guidelines [10]:

- Prior nivolumab + ipilimumab: TKI (cabozantinib, axitinib, lenvatinib + everolimus), HD IL-2;
- Pembrolizumab + axitinib: cabozantinib, lenvatinib + everolimus, HD IL-2.

Summary

Changes in first-line therapy will considerably change our current treatment approach. While guidelines recommend the use of TKIs after the failure of checkpoint inhibitors either with or without axitinib, the level of evidence to support these recommendations is low. With focus on the indication, sunitinib remains the only TKI with a label broad enough to cover its second-line use after failure of first-line checkpoint inhibitor therapy. However, data to support this strategy remains anecdotal. Cabozantinib is active after previous TKI failure and its pivotal trial only included a few patients with prior immunotherapy (Table 3). Additional evidence supports the idea that cabozantinib is active after prior checkpoint-inhibitor therapy, which also applies to other TKIs [55,59–61,63–65]. For instance, tivozanib was effective as a third-line therapy after checkpoint-inhibitor treatment in the prospective TIVO-3 study (Table 3) [67]. In our opinion, cabozantinib has shown improved efficacy when compared with sunitinib [20,21] and therefore should be the preferred TKI in the second line. In a retrospective trial, it was shown that VEGFR-TKI monotherapy with axitinib, pazopanib, sorafenib or sunitinib was more effective in later lines when used after immunotherapy (checkpoint inhibitors) rather than the combination of immunotherapy and VEGFR-TKI [72]. An acquired resistance against VEGFR-TKIs might be the reason. Therefore, it might make sense to use a TKI after prior combined treatment of a checkpoint-inhibitor and a VEGFR-TKI, which can

overcome resistance mechanisms due to a broader mode of action, especially the inhibition of receptor tyrosine kinases such as MET and AXL – for example, cabozantinib [73,74]. The German S3-guideline, an evidence-based guideline, recommends cabozantinib rather than axitinib as second-line treatment after TKI failure [5]. However, there is no head-to-head data comparing axitinib and cabozantinib as second-line therapies. Although cabozantinib or any other TKI except sunitinib are not approved for treatment after failure of ipilimumab and nivolumab, they are the preferred choice in guidelines such as the ESMO (any TKI after nivolumab + ipilimumab) [2] or EAU guidelines (any VEGF targeted therapy that has not been used previously) [3]. Use of an axitinib-checkpoint inhibitor combination has less uncertainties regarding the label, although data remains scarce. In such cases, cabozantinib might be the preferred choice in the subsequent treatment line. While the combination of lenvatinib and everolimus after failure of immunotherapy is not commonly used, recent data suggest that combining the two substances may result in a relevant clinical benefit [68]. Given the heterogeneity in patient populations of the published series, no specific recommendation can be made, which is a reflection of the current guidelines. However, differences in safety profiles and response patterns may exist and should be used to tailor treatment to individual patients.

Recommendations, unaddressed topics

After TKI-failure in advanced ccRCC with favorable-risk, we recommend nivolumab monotherapy or cabozantinib. However, this fraction of patients will further diminish in the near future and will then represent a minority of cases only. After failure of the combination of axitinib and a checkpoint inhibitor, the second-line treatment strategy is less clear and remains to be evaluated. A TKI other than axitinib, for example, cabozantinib, would be the panelists' preferred choice based on the prospective Phase III trial data being available for cabozantinib in the second-line setting [51].

We suggest using a TKI after failure of nivolumab plus ipilimumab (intermediate- and poor-risk group). In our opinion, the preferred TKI in second-line is cabozantinib. However, label restrictions may apply. One can justify the treatment decision in favor of a TKI using the recommendations issued by the ESMO or EAU. If possible, patients should be included in ongoing TKI trials recruiting patients in whom checkpoint-inhibitors have failed, for example, the prospective Phase II trial CaboPoint [75].

We do not recommend nivolumab or mTOR inhibitor monotherapy as second-line therapy after PD-1 immune-checkpoint inhibitor-based first-line therapy. Everolimus can be an option in later lines, also in combination with lenvatinib.

In conclusion, therapy of the advanced ccRCC recently experienced tremendous changes. With approval of diverse immunotherapy combinations for first-line therapy, new standards evolved. While these changes affected second- and later-line therapies considerably, additional investigations and trials are necessary to enable informed treatment decisions and to prospectively classify patients based on molecular information.

Conclusion

The approval of immunotherapy combinations for treating advanced ccRCC changes first-line treatment standards. In clinical practice, we see both patients who substantially benefit from these treatments and patients who do not profit at all or who profit less substantially. In the near future, it will be important to find reliable biomarkers or clinical features to better select patients who will benefit from immunotherapy (combinations) the most and who can be spared from potential irAEs. Currently, it is being investigated whether it is possible to change tumor environments, so that a cold tumor not responding to immunotherapy may turn into a hot tumor responding to immunotherapy.

With the absence of further direct comparisons of treatment modalities as part of randomized Phase III trials, the value of prospectively collected "real world data" as part of interdisciplinary registries gain relevance, despite the fact that the ongoing COSMIC-313 trial compares the triplet combination of cabozantinib plus ipilimumab and nivolumab in comparison to ipilimumab and nivolumab in intermediate- and poor-risk patients which will clarify, if the TKI has an additional benefit compared with a dual checkpoint inhibitor strategy. In addition, this trial will determine the safety-risk benefit, which might be outbalanced by the high AE rate of an exaggerated triplet strategy.

For second- and later-line therapies, the much needed additional investigations and trials will be available to enable informed treatment decisions.

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Executive summary

Risk assessment

- We recommend evaluating each patient's risk/prognosis by using the IMDC score before selecting first-line treatment.

First-line treatment

- Immunotherapy combinations such as pembrolizumab or avelumab plus axitinib may be the future standard to treat favorable-risk advanced ccRCC. However, given the low adverse event rate in this patient population and their differences in clinical outcome between trials, additional follow-up is required.
- We recommend the combinations pembrolizumab plus axitinib or nivolumab plus ipilimumab to treat intermediate- or poor-risk advanced ccRCC. Axitinib plus avelumab may be another option, yet, the combination has not shown a significant survival benefit.

Biomarker

- It appears that PD-L1 expression may be a suitable parameter to guide the decision to either use a combination of two checkpoint inhibitors or a combination of checkpoint inhibitor and TKI. However, there is an urgent need for objective and reliable molecular biomarkers.

Second-line treatment

- After TKI-failure in favorable-risk advanced ccRCC, we recommend nivolumab monotherapy or cabozantinib in the second line. However, in cases with TKI treatment in higher risk-groups due to any reason a different sequence may be preferred.
- We suggest using a TKI after failure of nivolumab plus ipilimumab (intermediate- and poor-risk group). In our opinion, the preferred TKI in second-line is cabozantinib. However, label restrictions may apply.

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- **Although a Phase II trial, the provided data led to the implementation of the combination of lenvatinib/everolimus in the second-line setting in many guidelines. In addition, it demonstrated clearly, that the combination of Tyrosin-kinase inhibition and mTOR-inhibition is safe and effective.**

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