short review

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Second-line therapy in metastatic renal cell cancer—how do we treat after immuno-oncology drugs?

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Summary The treatment landscape of metastatic renal cell cancer (mRCC) is rapidly evolving. To date in 2019 twelve drugs are licensed for this indication, two more drugs are awaited to be introduced into our portfolio of treatment options by the end of the year. First-line treatment has robust clinical trial data and is clearly stated by the consensus guidelines. It consists either of a tyrosine kinase inhibitor (TKI) monotherapy for favorable risk patients—defined by the Heng or IMDC (International mRCC Database Consortium) score—or the immuno-oncology (IO) combination of ipilimumab and nivolumab (Ipi/Nivo) for intermediate- and poor-risk patients who are eligible for this treatment. To date we have a clearly positive phase III trial of a TKI-IO combination that was superior to standard of care with sunitinib in untreated metastatic patients independent of the risk group. Pembrolizumab and axitinib will be most likely introduced to the treatment landscape by the end of the year. Despite all these very enthusiastic treatment options in first line, subsequent treatment recommendations are missing due to the lack of data. Only retrospective data can be used as a tool to make the right choice after the use of an IO drug in first line.

Keywords Pembrolizumab · Checkpoint inhibitor · Tyrosine kinase Inhibitor · Nivolumab · Ipilimumab

Take-home messages

- First-line treatment of mRCC is clearly defined by current guidelines from urological and oncological societies (EAU [1, 2], ESMO [3] and NCCN [4]).
- Second-line treatment options after first-line TKIs are recommended from randomized phase III trials and include nivolumab [5] and cabozantinib [6], as well as everolimus and lenvatinib [7], axitinib [8] and everolimus [9] (lower evidence and recommendation of the last three options in the current ESMO 2019 guidelines [3]),
- Patients progressing after first-line ipilimumab and nivolumab have several TKI options, although prospective data comparing one TKI with another are missing. Efficacy from retrospective data has been reported with an ORR between 30 and 40% [10, 11].
- Recently the first-line combinations of pembrolizumab and axitinib [12], as well as avelumab and axitinib, have been licensed for all IMDC risk-group patients as first-line treatment option. Subsequent treatment recommendations cannot be made, due to the lack of prospective data. Response rates of TKIs following this combination appear to be lower, but the efficacy is comparable to historical data in this setting.
- Prospective studies after pretreatment with IO combinations in first line are urgently needed

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Introduction

Current standard-of-care second-line treatment mRCC 2019

Second-line treatment after sunitinib or pazopanib

Patients with good risk IMDC features will still receive a VEGF multikinase inhibitor as first-line treatment based on the current ESMO, EAU and NCCN guidelines. For these patients we have clear evidence from randomized phase III trials with nivolumab (Checkmate025) [5], cabozantinib (METEOR trial) [6] and a phase II trial with everolimus and lenvatinib [7]. Nivolumab and cabozantinib have the highest evi-

Table 1 Second-line results after IPI/NIVO or PDL-1/PD-1 + TKI

	n	First-line therapy	2nd-line TKI ORR (%), PFS and OS (months)	2nd-line TKI
Auvray M et al. (Eur J Cancer 2019) [17]	*N* = 33	IPI/NIVO	ORR 36% (PR: 36%, 36% SD)	Sunitinib (*n* = 17) Axitinib (*n* = 8) Pazopanib (*n* = 6) Cabozantinib (*n* = 2)
Barata PC et al. (Br J Cancer 2018) [13]	*N* = 33	IPI/NIVO	ORR 33% PFS: 7.6 months (95%CI: 3.6–11.6)	Axitinib (*n* = 16) Pazopanib (*n* = 9) Sunitinib (*n* = 4) Cabozantinib (*n* = 4)
		Bev/atezolizumab Avelumab/axitinib	ORR 25% PFS: 6.2 months (95% CI: 5.2–7.2)	
Shah AY et al. (Eur J Cancer 2019) [14]	*N* = 70	IPI/NIVO (47%)	ORR: 41.2% (1.5% CR, 39.7% PR) PFS: 13.2 months (95%CI: 10.1, NA) 1-year OS: 79.6% (95% CI: 70.2–90.3%)	Pazopanib (*n* = 19) Sunitinib (*n* = 6) Axitinib (*n* = 25) Cabozantinib (*n* = 20)
		PD-1/PDL-1 + BEV (36%)		
		PD-1/PDL-1 monotherapy (nivolumab or atezolizumab, 17%)		

IPI/NIVO Ipilimumab/Nivolumab, *ORR* Objective Response Rate, *PR* Partial Response, *SD* Stable Disease, *PFS* Progression-free Survival, *TKI* Tyrosine Kinase Inhibitor, *Bev* Bevacizumab, *OS* Overall Survival, *PDL-1* Programmed Cell Death 1 Ligand 1, *PD-1* Programmed Cell Death Protein 1

dence level in these patients. The choice of treatment is mostly driven by the response on the first-line TKI and the adverse events that have been experienced during the first-line TKI treatment.

Second-line treatment after cabozantinib

Cabozantinib is an oral multiple kinase inhibitor which targets besides VEGF also AXL and MET and has been approved initially for second-line treatment after sunitinib failure, being superior to everolimus in the phase III METEOR study. In treatment naive intermediate and poor risk patients, cabozantinib showed an improved PFS of 8.6 months (95% CI: 6.8, 14.0) vs 5.3 months (95%CI: 3.0, 8.2) over sunitinib with a HR of 0.48. The FDA and EMA extended the approval of cabozantinib in December 2017 based on the PFS benefit. Certain limitations have been discussed in the CABOSUN trial [13], especially the underperformance of sunitinib patients in the control arm. In clinical practice cabozantinib is an option for intermediate and poor risk patients who are not candidates for ipilimumab and nivolumab. The toxicity profile of cabozantinib must be kept in mind when using this drug.

Second-line treatment after tivozanib (not applicable for USA—no FDA approval)

Tivozanib is a modern multi-VEGF receptor inhibitor (VEGFR1-3) with a short half-life and the highest IC_{50} of all TKIs for VEGF. It inhibits less "off targets", such as c-kit or FLT-3 and therefore has a better side effect profile. Tivozanib was licensed in 2017 by the EMA with a positive phase III trial against sorafenib, already published in 2013 [14]. Tivozanib is an option in the recently updated ESMO Guidelines as first-line treatment in all IMDC risk groups and therefore another monotherapy option for patients that are not suitable for an IO–IO combination. Only 13% of patients received subsequent treatments after tivozanib in the TIVO-1 trial and due to the early trial finish in 2013, none of the modern TKIs or PDL-1 inhibitors were available. Therefore, we have no real efficacy data on second-line treatment after tivozanib. It seems reasonable to use the same drugs as recommended after pazopanib or sunitinib pretreatment, mainly nivolumab, cabozantinib or everolimus and lenvatinib.

Second-line treatment after ipilimumab and nivolumab

Second-line treatment after the combination of a PD-1 and CTLA4 inhibitor is clearly a TKI. Since 2006 the armamentarium of TKIs in mRCC has tremendously been extended. Which TKI to choose is tricky and has not been prospectively evaluated yet. The only data we have are retrospective data from a chart review of patients in the Checkmate 214 study [15]. These 33 patients on TKIs after Ipi/Nivo consisted of sunitinib (*n* = 17), axitinib (*n* = 8), pazopanib (*n* = 6) and cabozantinib (*n* = 2). Objective response on those second-line TKIs was 36%. All responses were partial responses, no complete responses have been reported. Another 39% presented with stable disease (SD), allowing a clinical benefit rate in two thirds of patients. There were no new safety concerns reported of TKIs in the setting after IO–IO treatment. Data on second-line treatment efficacy after IO-IO or IO-TKI combinations are summarized in table 1.

Second-line treatment after PD-1/PDL-1 inhibitor (pembrolizumab or avelumab) and axitinib [12, 16]

Subsequent treatment in the Keynote-436 pembrolizumab plus axitinib vs sunitinib trial were reported to be cabozantinib or sunitinib [12]. The lack of data in this patient group after IO and TKI leaves us completely in the dark with what to offer these patients after a real progression or nonresponse on these two drugs. Small retrospective reports show a decent, but less high ORR than after Ipi/Nivo. Unfortunately, due to the limited use, we have no data on lenvatinib and everolimus after axitinib and a PD1/PDL-1 inhibitor. Targeting mTOR and FGFR is a logic concept

after failure of a selective VEGFR TKI and a checkpoint inhibitor.

A very recent retrospective report from the MD Anderson Cancer Center and Memorial Sloan Kettering Center including 70 patients with mixed first-line treatments including a PD1/PDL-1 or CTLA4 inhibitor showed comparable antitumor activity and tolerance to historic data [11].

Conclusions and future directions

The changing paradigm in first line for intermediate and poor risk IMDC patients treated with Ipi/Nivo and the upcoming change in the treatment of "all comers" with pembrolizumab and axitinib or avelumab axitinib needs a redefinition of the subsequent treatment algorithm.

Response rates, PFS and OS as well as safety suggests a sustained benefit of TKIs in second line after the use of an IO doublet. These results are in line with the published historical efficacy data of these drugs in first line.

Prospective second-line trials are currently not running after IO/IO or PD-1/L1 plus TKI. We are in urgent need for trial designs in this setting. Until then, we cannot make any clear recommendations with high evidence in second-, line treatment after the use of an IO combination with PD-1/PDL-1 or a TKI.

In summary we have 12 approved drugs in mRCC. The goal should be to offer as many drugs as possible during the treatment of disease. Every line must be newly defined depending on the severity of progression, duration of response in first line, experienced and remaining toxicity and the treatment goal and need for response (stable disease or rapid tumour shrinkage). In Austria we have proven in a recent chart review that we have been doing an excellent job in treating patients with mRCC in the TKI era by offering multiple treatment lines [17]. These exciting drug combinations including an IO treatment should encourage us to perform even better in the future.

Conflict of interest U. Vogl declares that she has no competing interests.

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