Ther Adv Med Oncol
2020, Vol. 12: 1–11
DOI: 10.1177/1758835920915303

Pazopanib as a possible option for the treatment of metastatic non-clear cell renal carcinoma patients: a systematic review

Melissa Bersanelli, Matteo Brunelli, Letizia Gnetti, Umberto Maestroni and Sebastiano Buti

Abstract

Background: Effective systemic treatment of non-clear cell renal carcinoma (nccRCC) is still an unmet clinical need, with few studies to support an evidence-based approach. To date, the only recommended standard first-line treatment is sunitinib. Pazopanib may also be used in nccRCC but its place in therapy is not clearly established. It has comparable efficacy and better tolerability than sunitinib in clear cell renal carcinoma. Our objective was to review the use of pazopanib in metastatic nccRCC.

Methods: We conducted a systematic review according to PRISMA guidelines. Any type of study reporting the use of pazopanib in metastatic renal cell carcinoma including cases with non-clear cell histology was eligible.

Results: In all, 15 studies were included in our analysis, including a total of 318 nccRCC patients treated with pazopanib. Most studies were retrospective ($n = 12$); three were prospective trials. The specific outcomes of nccRCC patients were reported by four studies. Pazopanib alone as first-line treatment gave overall response rates ranging from 27% to 33%, disease control rates of 81–89%, median progression free survival of 8.1–16.5 months and median overall survival of 17.3–31.0 months. Grade 3–4 adverse events rates were 21–55%.

Conclusion: The present review provides for the first time a systematic summary of evidence about the possible use of pazopanib as first-line treatment for nccRCC, with a favorable outcome despite the low strength of evidence. Pazopanib could be considered as a possible therapeutic option in this setting.

Keywords: anti-VEGF, chromophobe, non-clear cell renal carcinoma, papillary, pazopanib

Received: 28 November 2019; revised manuscript accepted: 4 March 2020.

Correspondence to:
Sebastiano Buti
Medical Oncology Unit, University Hospital of Parma, Via Gramsci 14, Parma, 43126, Italy
sebabuti@libero.it

Melissa Bersanelli
Medical Oncology Unit, University Hospital of Parma, Parma, Italy
Department of Medicine and Surgery, University of Parma, Parma, Italy

Matteo Brunelli
Department of Pathology, University of Verona, Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy

Letizia Gnetti
Pathologic Anatomy Unit, University Hospital of Parma, Parma, Italy

Umberto Maestroni
Urology Unit, University Hospital of Parma, Parma, Italy

Introduction

Non-clear cell renal carcinoma (nccRCC) represents a pool of heterogeneous diseases, in reality no more similar to each other than to clear cell renal carcinoma (ccRCC). According to the International Society of Urologic Pathologists/World Health Organization (ISUP/WHO) 2016 classification, the term "clear cell" is reserved for the tumor diagnostic entity characterized by morphological, immunophenotypical, and molecularly distinct characteristics such as clear cell aspects, most CAIX, CD10, cathepsin-k, and PAX-8 positive for immunoexpression and affected by *VHL* gene mutation.[1] The spectrum of the ccRCC "entity" shows a wide range of morphology, sometimes with the absence of clear cells, but still characterized by the driver *VHL* mutation. Instead, for nccRCC, the initial oncogenic event for nccRCC is not *VHL*-driven, and *VHL* mutations are less common among the classical non-clear histologies of chromophobe, collecting duct, medullary and unclassified RCC, with these classical non-clear histologies accounting for approximately 20% of all RCC cases.[2] Along with these classical non-clear histologies, the discovery of "apparent ccRCC" with no *VHL*

mutation and activation of other molecular pathway led to their recognition as non-clear cell entities, which, irrespective of the presence of cells with clear cytoplasm, maintain *VHL* function and are driven by Xp11 and TFEB rearrangements (translocation MiTF family RCC) or mutations in other molecules such as in succinate dehydrogenase-deficient RCC, acquired cystic kidney disease-associated RCC, clear cell-papillary RCC, and tubulocystic RCC.[1] Most tumors show an apparent ccRCC morphological phenotype, thus the routine use of an immunohistochemical panel is needed to rule out ccRCC *versus* nccRCC.[3]

The systemic treatment of advanced or metastatic nccRCC (mRCC) is supported by very scarce evidence, composed largely of retrospective or small phase II studies and subgroup analyses of expanded access program (EAP) studies or prospective trials in patients with any RCC histologies.[4] According to the National Comprehensive Cancer Network (NCCN) guidelines, the current recommendations for nccRCC systemic treatment are enrollment in a clinical trial or treatment with the vascular endothelial growth factor receptor (VEGFR)-inhibitor sunitinib as the preferred regimen.[5] Indeed, sunitinib is currently the only evidence-based choice in such minor histologies, based on evidence from some published studies (including phase II trials) and from the large number of nccRCC patients treated with this drug in the EAP.[4] Evidence from the prospective clinical trials ESPN (Everolimus *versus* Sunitinib Prospective Evaluation in Metastatic Non-Clear Cell Renal Cell Carcinoma) and ASPEN (Everolimus *versus* Sunitinib For Patients With Metastatic Non-Clear Cell Renal Cell Carcinoma), which were designed initially to demonstrate the superiority of everolimus, and the RECORD-3 trial (which included 66 patients with non-clear cell histology), supports the use of first-line sunitinib followed by second-line everolimus as the standard sequence for nccRCC patients, despite possibly biased results.[6–9]

Other drugs approved for mRCC treatment investigated in non-clear cell histologies include the mTOR inhibitors temsirolimus and everolimus, and the VEGFR-inhibitor sorafenib.[10–13] Nevertheless, such drugs probably do not represent the best first-line treatment option in the current landscape of systemic treatment for renal cancer, being superceded by immune checkpoint inhibitors (CKI) and novel tyrosine kinase inhibitors (TKI), used alone or in various combinations.

While sunitinib may still be a favorable treatment option for the clear cell mRCC population, at least from an actuarial risk point of view according to the International Metastatic RCC Database Consortium (IMDC) model, the true alternative to sunitnib is represented by pazopanib. This VEGFR-TKI is known to be noninferior to sunitinib in terms of efficacy, and has the advantages of favorable safety and quality-of-life profiles,[14,15] rendering pazopanib still an interesting alternative to be considered even for variant histologies, as suggested by NCCN guidelines.[5]

On the other hand, the new frontier in renal cancer treatment, represented by immunotherapy with CKIs alone (nivolumab) or in combination with each other (nivolumab plus ipilimumab) or with a TKI (axitinib plus pembrolizumab or avelumab), is still at the experimental stage in nccRCC patients, since non-clear cell histologies were excluded from the pivotal trials.[16–19] The use of immunotherapy for nccRCC is currently restricted to clinical trials, although preliminary results (e.g. with pembrolizumab alone) seem to be promising.[20] In the meanwhile, we should exploit the weapons at our disposal, balancing the (often scarce) amount of evidence with the expected benefits in terms of tolerability and safety.

With the present systematic review, we aimed to report the use of pazopanib in advanced/metastatic nccRCC across the literature, to summarize and provide evidence to possibly support its activity and feasibility in this neglected subgroup of renal cancer patients.

Methods

Search strategy and inclusion criteria

We followed PRISMA guidelines for this systematic review.[21] We searched PubMed for studies published in English language from the inception of each database to 6 August 2019 (see Supplementary Materials for full details). Two investigators (MeB and SB) independently searched the databases. The search terms were [“Carcinoma, Renal Cell”(MeSH) AND “Pazopanib”(Supplementary concept)]. The choice for such a wide search aimed to provide data about the entire pool of publications potentially including patients with nccRCC histology, even as a small subgroup from the overall population considered in each study. After the last selection of publications, we

screened all the references of the included articles for the recovery of any further eligible publications. Furthermore, we screened NCCN guidelines (Version 2.2020) for relevant references on pazopanib in nccRCC.[5]

Meetings libraries from American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) websites were also screened for further relevant publications (abstract and posters at international meetings), using the search terms "pazopanib" AND "non-clear cell renal carcinoma" OR "papillary renal carcinoma renal carcinoma" OR "chromophobe renal carcinoma" or "collecting duct renal carcinoma" OR "sarcomatoid renal carcinoma" OR "translocation-type carcinoma" OR "medullary renal cell carcinoma" OR "variant histology renal carcinoma".

Any type of study reporting the use of pazopanib in mRCC including cases with non-clear cell histology was eligible. Non-clear cell histology was defined as any of the following: chromophobe RCC, papillary RCC, collecting duct/Bellini's RCC, sarcomatoid RCC intended as purely sarcomatoid or with predominant sarcomatoid component (ccRCC with sarcomatoid features was excluded), translocated RCC, medullary RCC or any unspecified non-clear cell histologic variant. We included retrospective studies and prospective trials or case series reporting at least five patients with nccRCC treated with pazopanib. Studies with less than five pazopanib-treated nccRCC patients, single case reports, and reviews without meta-analysis were excluded. Two investigators (MeB and SB) independently reviewed the retrieved publications to select the pertinent articles; disagreements were resolved with the consensus of a third investigator (MaB). Two reviewers (MeB and SB) independently extracted study data; any discrepancies or disagreements were resolved by consensus between all study authors.

As a separate explorative search, we checked clinicaltrials.gov for any trial ongoing with pazopanib in an nccRCC patient population.

Data extraction

The following information was extracted from each study by MeB and SB: first author, year of publication, study type, overall study population (type and number of patients) and setting, number of patients with nccRCC treated with pazopanib and respective histology, line of therapy, primary endpoint/objectives and, if available, pazopanib treatment outcomes in nccRCC patients. We included only the most updated and complete report (full text over posters/abstracts) of any studies when duplicate publications were identified. No statistical analysis was planned due an expected high level of heterogeneity between included studies; instead, findings are descriptive.

Results

Search results

Our search retrieved 305 publications, from which we selected 125 potentially relevant titles for more detailed evaluation (Figure 1). After abstract reading, 61 publications were selected for full-text screening. All their references were screened and a further six publications were included for full-text screening; moreover, another study was recovered from the bibliography of the NCCN guidelines.[5] In total, the full text of 68 studies was screened; of these, 13 studies published between 2014 and 2018 met our inclusion criteria and were included in the review.[22–34] In addition, eight potentially relevant studies were found as abstract or posters in the ESMO database, of which six were excluded: three were duplicates of fully published articles and three lacked data on histology or had fewer than five nccRCC patients. Two abstracts/posters were included in the review.[35,36] Only three potentially pertinent studies were selected from ASCO presentations, but all were excluded (two were duplicates of fully published articles and one did not include any nccRCC patients). Finally, 15 studies were included in the present review, with a total of 318 nccRCC patients treated with pazopanib.[22–36]

Study characteristics

The heterogeneity was high. Most of the included studies were retrospective ($n = 11$); one was a retrospective analysis on prospective patient population; the prospective trials ($n = 3$) included a phase I study, a phase II trial, and a phase IIIb study. No meta-analyses were found. Ten studies included patients with mRCC with different histologies, including ccRCC and nccRCC, while five were conducted in a specifically selected nccRCC patient population. Seven studies included the use of different types of TKI, eight investigated pazopanib (seven as monotherapy and one in combination with another drug). The majority of the studies that included both clear cell and non-clear

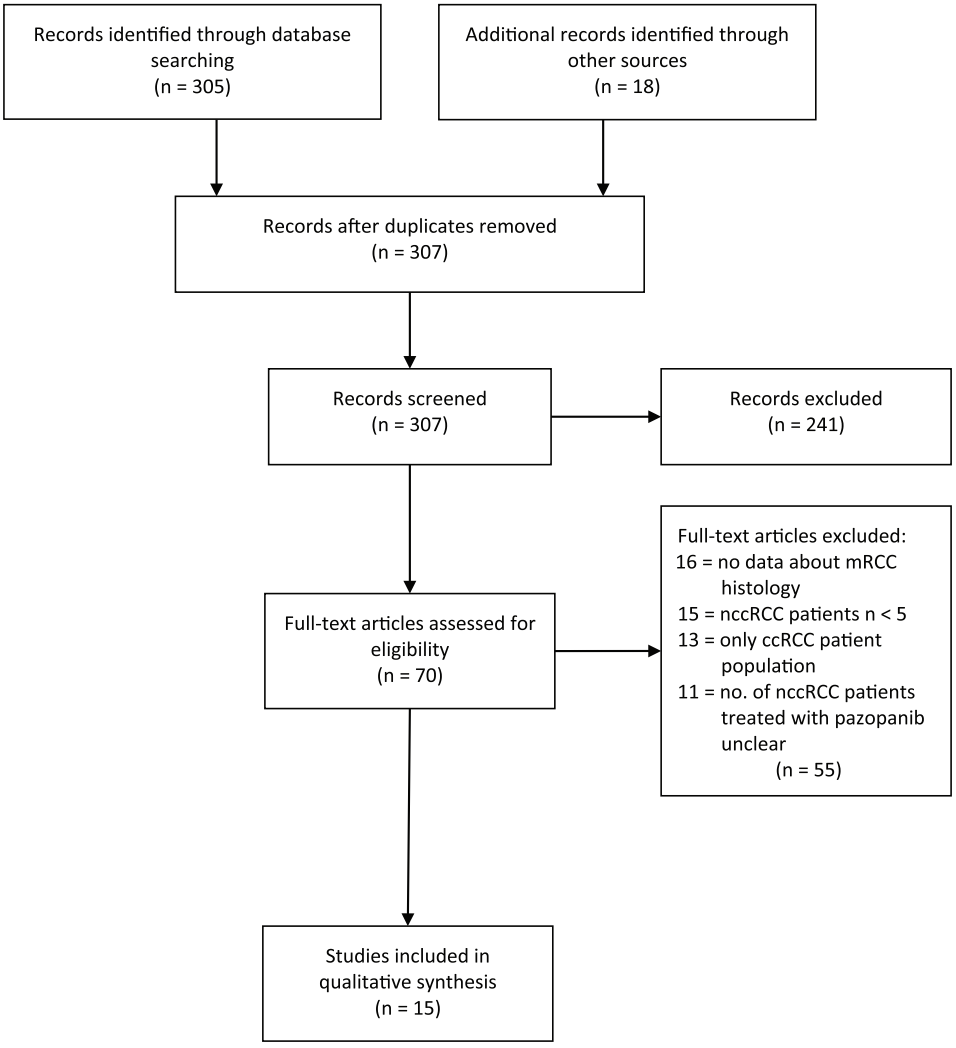

Figure 1. Flowchart depicting study selection according to the (PRISMA) statement.
ccRCC, clear cell renal carcinoma; mRCC, metastatic nccRCC; nccRCC, non-clear cell renal carcinoma; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

cell histologies did not report the outcomes according to the histologic subtype: the only data we could obtain in most of the cases was the number of nccRCC patients receiving pazopanib within the overall patient population. The size of the nccRCC patient population treated with pazopanib across all studies ranged between 6 and 42 patients. The characteristics of the included studies and outcomes data of interest are reported in Table 1.

Treatment outcomes

Pazopanib treatment outcomes in nccRCC patients were reported in only four studies.[22,23,26,29] Pazopanib alone as first-line treatment was associated with overall response rates (ORR) of 27% to 33%, disease control rates (partial/complete responses plus stable disease) of 81% to 89%, median progression free survival (PFS) ranging from 8.1 to 16.5 months, and median overall survival (OS) from 17.3 to 31 months.[23,26,29] The rate of grade 3–4 (G3-4) adverse events ranged from 21% to 55%.[22,23,26,29] Of interest, the study with pazopanib plus another agent (the histone deacetylase inhibitor abexinostat) was the only one to compare the ORR of nccRCC patients (17%) with that of ccRCC patients (31%); in this study, the histologic subtype was exclusively papillary RCC.[22]

Table 1. Publications included in the review.

Author of publication and trial name	Study design	Patients (*N*)	Treatment arm/s	nccRCC patients treated with pazopanib (*n*)	nccRCC histologic subtype (*n*)	Line of therapy with pazopanib	Endpoints or objectives (overall population)	Outcome of nccRCC patients treated with pazopanib
Escudier *et al.*[24] PISCES	Randomized, controlled, double-blind, cross-over, phase IIIb prospective trial	mRCC, treatment naïve (*N* = 168)	Pazopanib followed by sunitinib *versus* Sunitinib followed by pazopanib	12	Papillary (*n* = 6) chromophobe (*n* = 2) other (*n* = 4)	1st	Patient preference for a specific treatment (primary endpoint)	NR
Vogelzang *et al.*[34]	Retrospective analysis from US electronic database	mRCC (*N* = 177)	Pazopanib (followed by mTOR inhibitor as second line in 35 patients)	32	NR	1st	OS, PFS, AEs, treatment patterns, healthcare resource use	NR
Pérez-Valderrama *et al.*[31] SPAZO	Nation-wide, retrospective, observational study	mRCC (*N* = 278)	Pazopanib	18	NR	1st	Effectiveness of pazopanib in clinical practice and validation of the IMDC model in this setting	NR
Kim *et al.*[27]	Single center, retrospective study	mRCC, poor risk features (*N* = 172)	Pazopanib (*n* = 72) or sunitinib	7	Papillary (*n* = 3) others (*n* = 3) unclassified (*n* = 1)	Prior immunotherapy permitted; prior anti-VEGF therapy excluded	Efficacy and safety of sunitinib and pazopanib in the poor-risk population	NR
Ruiz-Morales *et al.*[33]	Retrospective population-based analysis from the IMDC database	mRCC (*N* = 7438)	Pazopanib (*n* = 919) or sunitinib	29	NR	1st	OS, PFS, ORR, performed proportional hazard regression adjusting for IMDC prognostic groups, OS2, PFS2	NR
Joshi *et al.*[25]	Single center, retrospective study	mRCC (*N* = 28)	Pazopanib	8	NR	1st	ORR, PFS, AEs, discontinuations and dose reductions	NR
Aggarwal *et al.*[22] NCT01543763	Single arm, open label, phase I prospective trial	solid tumors (*N* = 51), including mRCC patients on dose expansion (*n* = 22)	Pazopanib plus abexinostat	6	papillary (*n* = 6)	any	DLT, MTD, AEs, ORR	ORR = 17% (*versus* 31% in ccRCC patients)
Matrana *et al.*[29]	Single center, retrospective study	Metastatic nccRCC (*N* = 29)	Pazopanib	29 (overall study population)	Papillary (*n* = 7) chromophobe (*n* = 4) unclassified (*n* = 5) others (collecting duct, translocation Xp11.2, sarcomatoid) (*n* = 13)	any	ORR, PFS, OS, AEs	1st line: mPFS = 8.1 months; mOS = 31 months; ORR = 33%; subsequent lines: mPFS = 4.0 months, OS = 13.6 months; ORR = 6% G3-4 AEs (overall) = 21%

(Continued)

Table 1. (Continued)

Author of publication and trial name	Study design	Patients (*N*)	Treatment arm/s	nccRCC patients treated with pazopanib (*n*)	nccRCC histologic subtype (*n*)	Line of therapy with pazopanib	Endpoints or objectives (overall population)	Outcome of nccRCC patients treated with pazopanib
Buti *et al.*[23] PANORAMA	Multicenter, retrospective study	Metastatic nccRCC (*N* = 37)	Pazopanib	37	Papillary (*n* = 19) chromophobe (*n* = 9) 1 Xp11.2 translocation (*n* = 1) unclassified (*n* = 8)	1st	ORR, DCR, PFS, OS, safety	ORR = 27%; DCR = 81%; mPFS = 15.9 months; mOS = 17.3 months; G3-4 AEs = 32%
Pal *et al.*[30]	Multicenter, retrospective study	mRCC (*N* = 1173)	Pazopanib (*n* = 165) Other TKI or mTOR inhibitors	42	NR	2nd	Assessment of real-world treatment patterns of targeted therapies after failure of first-line TKI	NR
Jung *et al.*[26] NCT01538238	Single arm, open label, phase II, multicenter, prospective study	Metastatic nccRCC, excluding collecting duct or sarcomatoid type (*N* = 29)	Pazopanib	29	Papillary (*n* = 19) chromophobe (*n* = 3) unclassified (*n* = 2) unknown (*n* = 5)	1st (*n* = 13) 2nd after mTOR inhibitor (*n* = 12) 2nd after immunotherapy (*n* = 2)	ORR (primary endpoint) DCR, PFS, OS, AEs (secondary endpoints)	ORR = 28% DCR = 89% mPFS = 16.5 months mOS = not reached (median follow-up 21.3 months) G3-4 AEs = 55%
Poprach *et al.*[32]	Retrospective registry-based analysis (RENIS registry)	mRCC (*N* = 426)	Pazopanib	19	NR	1st (but prior cytokines permitted)	PFS, OS, ORR, DCR, survival according to IMDC and MSKCC models	NR
Masini *et al.*[28] CORE-URO-01	Multicenter, retrospective study	mRCC (*N* = 229)	Pazopanib	19	NR	1st	Effect of kidney function on treatment outcomes (PFS, OS)	NR
Rodriguez Lajusticia *et al.*[35] ESMO	Multicenter, retrospective study	nccRCC (*N* = 173)	Any systemic or local treatment	16	Papillary (*n* = 96) chromophobe (*n* = 24) sarcomatoid (*n* = 40) others (*n* = 13)	1st	Baseline clinical features, histologic subtypes, therapeutic management and survival status	NR
Staehler *et al.*[36] ESMO	Retrospective analysis on prospective registry	Papillary mRCC (*N* = 92)	TKI or mTOR inhibitors	15	papillary (*n* = 92)	1st and 2nd	Treatment patterns, PFS, OS	The use of pazopanib as first line increased from 2007 to 2016 (other outcomes NR)

AEs, adverse events; ccRCC, clear cell renal-cell carcinoma; DCR, disease control rate; DLT, dose limiting toxicity; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mRCC, metastatic renal-cell carcinoma; MSKCC, Memorial Sloan Kettering Cancer Center; MTD, maximally tolerated dose; nccRCC, non-clear cell renal-cell carcinoma; NR, not reported; ORR, objective response rate; OS, overall survival; OS2, second-line OS; PFS, progression free survival; PFS2, second-line PFS; TKI, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor.

Discussion

To the best of our knowledge, this is the first systematic review investigating the use of pazopanib in nccRCC. The first element we came across was the fact that the majority of studies that included a non-clear cell subpopulation completely missed reporting findings for this subgroup of patients; most did not provide results separately according to histology. Beyond the lost opportunity to offer some evidence on the treatment of patients with rare histologies, this constitutes a bias potentially affecting the overall results of such studies within the overall population enrolled, especially given the possible prognostic and/or predictive impact of the ccRCC histologic type.[1,37]

The limitations of the present analysis are the heterogeneity of the included studies, the limited number of studies with available efficacy data, and the retrospective nature of most of these studies. These limitations may contribute to interpretation bias.

Nevertheless, our analysis provided some useful and favorable elements. First, pazopanib as first-line treatment seems to be consistently associated with an ORR of around 30%. Furthermore, the outcomes of nccRCC patients in terms of PFS and OS showed median values between 8.1 and 16.5 months for PFS, and up to 31 months for OS, which are strongly consistent with those historically known for ccRCC.[14,15] Such outcomes are also comparable with those obtained with sunitinib in nccRCC populations.[4,6–9] In addition, the toxicity profile of pazopanib in this subgroup did not appear to be worse than that observed in the pivotal trials of pazopanib in the ccRCC patient population.[14,15] On the other hand, the only prospective comparative data between the two drugs have been provided by two studies including ccRCC patients only.[14,24] Such trials demonstrated similar efficacy and toxicity for sunitinib and pazopanib, with a particularly favorable tolerability for the latter.[14,24] In comparative studies, patients receiving sunitinib were more likely to develop fatigue, hand-foot syndrome, or thrombocytopenia compared with pazopanib, while patients receiving pazopanib were more likely to develop elevated liver enzyme levels.[14] Health-related quality of life was higher in the pazopanib than the sunitinib group.[14]

In the light of such results, in which scenario should nccRCC patients receive pazopanib as the first-line treatment of choice? Of interest, in exploratory analyses from the ASPEN trial, sunitinib was associated with better PFS in patients with favorable or intermediate risk according to Memorial Sloan Kettering Cancer Center (MSKCC) criteria and in those with papillary or unclassified histology.[9] In parallel, it should be investigated whether pazopanib should be preferentially offered to patients with other histologic subtypes less responsive to sunitinib. On the other hand, pazopanib may represent a more feasible option for frail or elderly patients considering its good tolerability profile.

NccRCC histotypes still represent a major challenge from a therapeutic standpoint. The authors of an interesting meta-analysis found a negative predictive value of non-clear histology for systemic treatment efficacy in general, with lower response rates, and worse PFS and OS compared with ccRCC; the authors concluded that optimal therapy for patients with non-clear histologies remains to be established.[4] Evidence from the present review reinforces this paradigm, as exemplified in the study with pazopanib plus abexinostat, in which the ORR of papillary RCC patients was half that compared with ccRCC patients. On the other hand, our findings seem to be reassuring about the outcome of nccRCC patients treated pazopanib alone. Moreover, across comparative studies, it is hard to determine whether differences in outcomes between nccRCC and ccRCC are due difference in treatment efficacy or to the different biologic behavior of the disease, since it is known that the histologic subtype also influences prognosis.[37]

On the other hand, new therapies have been recently investigated in advanced nccRCC patients, including immunotherapeutic compounds. The phase II KEYNOTE-427 study of pembrolizumab first-line monotherapy demonstrated an encouraging antitumor activity in the nccRCC cohort (ORR 25.4%).[20] Further trials are currently ongoing, such as UNISoN (www.clinicaltrialsgov NCT03177239) and SUNIFORECAST (NCT03075423), both of which are investigating nivolumab with or without ipilimumab in patients with nccRCC. Some of them have preliminary results, with ORR 26% in the nccRCC population for bevacizumab and atezolizumab (NCT02724878),[38] and ORR 32% for previously untreated patients in the CALYPSO trial (NCT02819596), which combines savolitinib with durvalumab in patients with papillary

Table 2. Trials in progress with the use of pazopanib in advanced non-clear cell renal carcinoma patients.

Trial number and/or name	Study design	Phase	Disease	Setting	Treatment arms	Estimated enrollment (*N*)	Primary endpoint	Start date	Estimated completion date
NCT01767636[43]	Multicenter, single arm, open label	II	Advanced nccRCC (all subtypes)	First or second line	Pazopanib	38	12-month OS rate	2013	2020
NCT01538238[44]	Single center, single arm, open label	II	Advanced nccRCC (excluding collecting duct and sarcomatoid)	TKI naïve patients (prior immunotherapy permitted)	Pazopanib	10	ORR	2012	2015*

nccRCC, non-clear cell renal-cell carcinoma; ORR, objective response rate; OS, overall survival; TKI, tyrosine kinase inhibitors.
*Completed but not yet published.

RCC.[39] Such data suggest similar activity of such new compounds compared with that of pazopanib in the same setting.

Advances in the development of tailored strategies for nccRCC, again mostly observed for the apparent clear cell tumors, are eagerly awaited, especially in the light of the recent identification of their genomic basis and their molecular characterization.[40,41] The inclusion of nccRCC, that is, chromophobe, papillary and medullary subtypes of RCC is outside the scope of current knowledge, and, given the spectrum of biology of newly described entities does not permit their inclusion in the same basket of clinical trials in RCC. Pioneering clinical trials with central identification/classification of tumor histotype including the minimum standards relating to new tumor classification would be welcome.[3] New entities (non-clear entities) do express a wide range of angiogenic promoters, thus promising different responsiveness to anti-angiogenic drugs, and also express a wide range of tumoral immune enrichment, again offering a promising target for different immunotherapies.

Trial design for pazopanib in patients with nccRCC should be based first on immunophenotypical and molecular analysis of patient tumors, by using CK7, CD10, CD13, PAX-8, HMB45, SDH, cathepsin-k, parvalbumin, and S100A1, with subsequent *VHL*, chromosome 3p and Xp11, TFEB gene analysis. Large studies of major tumor subtypes have confirmed the varying clinical behavior of the various morphotypes of renal epithelial neoplasia. Newly described nccRCC morphotypes have a different prognosis to ccRCC morphotypes, thus treatment protocols should be specific for tumor morphotype.[42]

Of note, at least two trials with pazopanib in this population seem to be ongoing (one completed, but not yet published; Table 2).[43,44] Despite their small sample size, they will provide prospective data in a specifically selected nccRCC patient population, potentially offering more strength to the current evidence for the use of pazopanib in this setting.

Conclusion

The systemic treatment of nccRCC is still an unmet clinical need, with few studies in support of an evidence-based choice and terse guidelines. To date, the main recommendation for a standard first-line treatment supported enough to

reach clinical practice is represented by sunitinib, whilst the strength of evidence being minor for pazopanib as an alternative.[4,5] Nevertheless, the comparability of pazopanib with sunitinib in terms of efficacy for ccRCC patients is demonstrated, as well as its better tolerability, and the present review provides at least a systematic summary of evidence about its possible use as first line treatment for nccRCC, with favorable outcome despite low strength of evidence. On this basis, we suggest that pazopanib could be considered as a possible good therapeutic option in this setting, aiming to a patient-tailored rather than an exclusively histology-tailored clinical strategy.

Acknowledgements

We thank Tracy Harrison of Springer Healthcare, who edited the article prior to submission. Support for the medical editing was provided by Novartis.

Conflict of interest statement

Melissa Bersanelli received honoraria as speaker at scientific events by Bristol-Myers Squibb (BMS) and Pfizer; as consultant for advisory role by Novartis, Mundipharma, BMS, and Pfizer; as medical writer by Mundipharma; she also received research funding from Seqirus UK, Pfizer, Novartis, BMS, MSD, Astra Zeneca, Roche, and Sanofi Genzyme.

Sebastiano Buti received honoraria as speaker at scientific events and advisory role by Bristol-Myers Squibb (BMS), Pfizer; MSD, Ipsen, Roche, Eli-Lilly, AstraZeneca, and Novartis.

Matteo Brunelli, Letizia Gnetti, Umberto Maestroni have no conflict of interest to declare.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Support for the medical editing was provided by Novartis.

ORCID iDs

Melissa Bersanelli https://orcid.org/0000-0002-6527-6281

Sebastiano Buti https://orcid.org/0000-0003-0876-0226

Supplemental material

Supplemental material for this article is available online.

References

1. Delahunt B, Cheville JC, Martignoni G, *et al.* The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. *Am J Surg Pathol* 2013; 37: 1490–1504.
2. Li ZC, Zhai G, Zhang J, *et al.* Differentiation of clear cell and non-clear cell renal cell carcinomas by all-relevant radiomics features from multiphase CT: a VHL mutation perspective. *Eur Radiol* 2019; 29: 3996–4007.
3. Warren AY and Harrison D. WHO/ISUP classification, grading and pathological staging of renal cell carcinoma: standards and controversies. *World J Urol* 2018; 36: 1913–1926.
4. Vera-Badillo FE, Templeton AJ, Duran I, *et al.* Systemic therapy for non-clear cell renal cell carcinomas: a systematic review and meta-analysis. *Eur Urol* 2015; 67: 740–749.
5. NCCN. Clinical practice guidelines in oncology. Kidney cancer. Version 2.2020, www.nccn.org (2019, accessed 6 August 2019).
6. Armstrong AJ, Halabi S, Eisen T, *et al.* Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. *Lancet Oncol* 2016; 17: 378–388.
7. Buti S and Bersanelli M. Non-clear-cell renal carcinoma therapy: handle with care. *Lancet Oncol* 2016; 17: 270–271.
8. Motzer RJ, Barrios CH, Kim TM, *et al.* Phase II randomized 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: 2765–2772.
9. Tannir NM, Jonasch E, Albiges L, *et al.* Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (ESPN): a randomized multicenter phase 2 trial. *Eur Urol* 2016; 69: 866–874.
10. Dutcher JP, de Souza P, McDermott D, *et al.* Effect of temsirolimus versus interferon-alpha on outcome of patients with advanced renal cell carcinoma of different tumor histologies. *Med Oncol* 2009; 26: 202–209.
11. Escudier B, Molinie V, Bracarda S, *et al.* Open-label phase 2 trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis. *Eur J Cancer* 2016; 69: 226–235.
12. Koh Y, Lim HY, Ahn JH, *et al.* Phase II trial of everolimus for the treatment of

nonclear-cell renal cell carcinoma. *Ann Oncol* 2013; 24: 1026–1031.

13. Stadler WM, Figlin RA, McDermott DF, *et al.* Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America. *Cancer* 2010; 116: 1272–1280.
14. Motzer RJ, Hutson TE, Cella D, *et al.* Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med* 2013; 369: 722–731.
15. Sternberg CN, Davis ID, Mardiak J, *et al.* Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010; 28: 1061–1068.
16. Motzer RJ, Escudier B, McDermott DF, *et al.* Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015; 373: 1803–1813.
17. Motzer RJ, Penkov K, Haanen J, *et al.* Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019; 380: 1103–1115.
18. Motzer RJ, Tannir NM, McDermott DF, *et al.* Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018; 378: 1277–1290.
19. Rini BI, Plimack ER, Stus V, *et al.* Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019; 380: 1116–1127.
20. McDermott DF, Lee JL, Ziobro M, *et al.* First-line pembrolizumab (pembro) monotherapy for advanced non-clear cell renal cell carcinoma (nccRCC): results from KEYNOTE-427 cohort B. *J Clin Oncol* 2019; 37(Suppl. 7): abstract 546.
21. Liberati A, Altman DG, Tetzlaff J, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009; 6: e1000100.
22. Aggarwal R, Thomas S, Pawlowska N, *et al.* Inhibiting histone deacetylase as a means to reverse resistance to angiogenesis inhibitors: phase I study of abexinostat plus pazopanib in advanced solid tumor malignancies. *J Clin Oncol* 2017; 35: 1231–1239.
23. Buti S, Bersanelli M, Maines F, *et al.* First-line pazopanib in non-clear-cell renal carcinoma: the Italian retrospective multicenter PANORAMA study. *Clin Genitourin Cancer* 2017; 15: e609–e614.
24. Escudier B, Porta C, Bono P, *et al.* Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. *J Clin Oncol* 2014; 32: 1412–1418.
25. Joshi A, Agarwala V, Ramaswamy A, *et al.* Initial experience with first-line pazopanib in the treatment of metastatic renal cell carcinoma: a single institution data. *Indian J Cancer* 2016; 53: 575–578.
26. Jung KS, Lee SJ, Park SH, *et al.* Pazopanib for the treatment of non-clear cell renal cell carcinoma: a single-arm, open-label, multicenter, phase II study. *Cancer Res Treat* 2018; 50: 488–494.
27. Kim JH, Park I and Lee JL. Pazopanib versus sunitinib for the treatment of metastatic renal cell carcinoma patients with poor-risk features. *Cancer Chemother Pharmacol* 2016; 78: 325–332.
28. Masini C, Vitale MG, Maruzzo M, *et al.* Safety and efficacy of pazopanib in first-line metastatic renal-cell carcinoma with or without renal failure: CORE-URO-01 study. *Clin Genitourin Cancer* 2019; 17: e150–e155.
29. Matrana MR, Baiomy A, Campbell M, *et al.* Outcomes of patients with metastatic non-clear-cell renal cell carcinoma treated with pazopanib. *Clin Genitourin Cancer* 2017; 15: e205–e208.
30. Pal SK, Signorovitch JE, Li N, *et al.* Patterns of care among patients receiving sequential targeted therapies for advanced renal cell carcinoma: a retrospective chart review in the USA. *Int J Urol* 2017; 24: 272–278.
31. Pérez-Valderrama B, Arranz Arija JA, Rodriguez Sanchez A, *et al.* Validation of the International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC) prognostic model for first-line pazopanib in metastatic renal carcinoma: the Spanish Oncologic Genitourinary Group (SOGUG) SPAZO study. *Ann Oncol* 2016; 27: 706–711.
32. Poprach A, Fiala O, Chloupkova R, *et al.* Pazopanib for metastatic renal cell carcinoma: a registry-based analysis of 426 patients. *Anticancer Res* 2018; 38: 449–456.
33. Ruiz-Morales JM, Swierkowski M, Wells JC, *et al.* First-line sunitinib versus pazopanib in metastatic renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur J Cancer* 2016; 65: 102–108.
34. Vogelzang NJ, Hackshaw MD, Hutson TE, *et al.* First-line and sequential use of pazopanib followed by mammalian target of rapamycin inhibitor therapy among patients with advanced renal cell carcinoma in a US community oncology setting. *Clin Genitourin Cancer* 2015; 13: 210–217.

35. Rodriguez Lajusticia L, Martín A, Pinto Marin A, *et al.* Retrospective analysis of metastatic non-clear cell renal carcinoma (NCCRC): the Spanish Grupo Centro Experience. *Ann Oncol* 2016; 27(Suppl. 6): 833P.

36. Staehler M, Müller L, Goebell PJ, *et al.* Treatment reality and outcome data of patients with advanced papillary renal cell carcinoma – data from the German prospective RCC-Registry *Ann Oncol* 2017; 28(Suppl. 5): 909P.

37. Zimpfer A, Glass A, Zettl H, *et al.* Renal cell carcinoma diagnosis and prognosis within the context of the WHO classification 2016. *Urologe A* 2019; 58: 1057–1065.

38. McKay RR, McGregor BA, Gray K, *et al.* Results of a phase II study of atezolizumab and bevacizumab in non-clear cell renal cell carcinoma and clear cell renal cell carcinoma with sarcomatoid differentiation. *J Clin Oncol* 2019; 37(Suppl. 7): abstract 548.

39. Powles T, Larkin JMG, Patel P, *et al.* A phase II study investigating the safety and efficacy of savolitinib and durvalumab in metastatic papillary renal cancer (CALYPSO). *J Clin Oncol* 2019; 37(Suppl. 7): abstract 545.

40. Cancer Genome Atlas Research Network, Linehan WM, Spellman PT, *et al.* Comprehensive molecular characterization of papillary renal-cell carcinoma. *N Engl J Med* 2016; 374: 135–145.

41. Davis CF, Ricketts CJ, Wang M, *et al.* The somatic genomic landscape of chromophobe renal cell carcinoma. *Cancer Cell* 2014; 26: 319–330.

42. Srigley JR and Delahunt B. Uncommon and recently described renal carcinomas. *Mod Pathol* 2009; 22(Suppl. 2): S2–S23.

43. ClinicalTrials.gov. Pazopanib hydrochloride in treating patients with metastatic kidney cancer. ClinicalTrials.gov Identifier: NCT01767636, www.clinicaltrials.gov (2019, accessed 11 August 2019).

44. ClinicalTrials.gov. pazopanib_NCRCC,Ph2 STUDY. ClinicalTrials.gov Identifier: NCT01538238, www.clinicaltrials.gov (2019, accessed 11 August 2019).