Editorial Commentary

Another one in the chamber: cabozantinib for patients with metastatic non clear cell renal cell carcinoma

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The term "Non-clear cell Renal Cell Carcinoma (nccRCC)" recognized a large series of renal tumours characterized of a specific genomic and morphological signature. Compared to clear cell renal cell carcinoma (ccRCC), these tumours are uncommon diagnoses with an overall incidence around 20–25% of primary kidney tumours) (1).

The last pathological classification of nccRCC (2016-World Health Organization) defines over a dozen of different histopathological entities (2).

Papillary renal cell carcinoma (pRCC) and Chromophobe Renal Cell Carcinoma (chRCC) are the most frequent subtypes (10–15% Prcc, 4–5% chRCC) of nccRCC while medullary, translocation and collecting duct RCC represent an infrequent diagnosis.

Although several efforts have been made to improve therapeutic options of patients with metastatic nccRCC, the clinical outcomes achieved resulted significantly worse when compared to those observed in metastatic ccRCC (1).

The main explication is due to the exclusion of nccRCC patients from clinical and treatment trials. Therefore, the majority of evidences regarding treatment management of these tumours derived from retrospective analysis and expanded access programs. Historically, metastatic nccRCCs have been treated in the same way of metastatic ccRCCs and very few interventional studies have been developed specifically for nccRCCs (*Table 1*).

This negative trend has been changed in last years mainly thanks to an increased knowledge of molecular and genomic behaviours of each tumour. Results provided by genomic analysis and The Cancer Genomic Atlas (TCGA) have significantly characterized this heterogeneous spectrum of tumours (3-6). In particular:

- Papillary renal cell carcinoma (pRCC) is a disease, which involve tumours associated to indolent course and favourable clinical outcomes (type I) and tumours associated to clinical aggressiveness and poor prognosis (type II). Alteration of the MET genes can be observed in over 80% of type I and about 45% of type II pRCC. These two tumours also shared often alteration in SETD2 (chromatin remodelling gene) and sometimes express alteration of EGFR gene. 9p loss, and CpG island methylator phenotype are two genomic findings associated to poor prognosis and are generally observed in type II pRCC (3-6).
- Chromophobe Renal Cell Carcinoma (ChRCC) is often associated to TP53 mutation (32%), mTOR (23%) and PTEN (9%). Of note chromosome loss

Table 1 Summary tables of prospective/retrospective series in nccRCC

Study name or first author	Drug/s	N	Line of treatment	Type of study	ORR	PFS	OS
ASPEN	Everolimus *vs.* Sunitinib	108	First	Prospective	Everolimus =8%; Sunitinib =18%	Everolimus =5.6 months (5.5–60); Sunitinib =8.3 (5.8–11.4)	Everolimus =13.2 (9.7–37.9); Sunitinib =31.5 (14.8–NA)
ESPN	Everolimus *vs.* Sunitinib	68	First/Second	Prospective	Everolimus =3%; Sunitinib =11%	Everolimus =4.1 months (2.7–10.5); Sunitinib =6.1 (4.2–9.4)	Everolimus =14.9 (8.0–23.4); Sunitinib =16.2 (14.2–NA)
RECORD 3	Everolimus *vs.* Sunitinib	66	First/Second	Prospective	NR	Everolimus =5.1 months (2.6–7.9); Sunitinib =7.2 (5.4–13.8)	NR
NCT00726323	Foretinib	74	First/Second	Prospective	13.5%	9.3 months (6.9–12.9)	Not reached
NCT02127710	Savolitinib	109	First	Prospective	18% (in MET +)	MET+ =6.2 months (4.1–7.0)	NR
ARCC NCT00065468	INF *vs.* Temsirolimus	73	First	Prospective	INF =12%; Temsirolimus =12%	INF=1.8 (1.6–2.1); Temsirolimus=7.0 (3.9–8.9)	INF =4.3 (3.2–7.3); Temsirolimus =11.6 (8.9–13)
RAPTOR	Everolimus	88	First	Prospective	1%	pRCC type I =7.9 (2.1–11); pRCC type II =5.1 (3.3–5.5)	pRCC type I =28.0 (7.6–NA); pRCC type II =24.2 (15.8–32.8)
SUPAP	Sunitinib	61	First	Prospective	NR	pRCC type I =6.6 (2.8–14.8); pRCC type II =5.5 (3.8–7.1)	pRCC type I =17.8 (5.7–26.1); pRCC type II =12.4 (8.4–14.3)
NCT01798446	Axitinib	40	Second/ Third	Prospective	37.5%	7.4 months (5.2–9.5)	12.1 months (6.4–17.7)
Martínez Chanzá N	Cabozantinib	112	All	Retrospective	27%	Time to treatment failure: 6.7 months (5.5–8.6)	12 months OS 51% (39–62%)
Pisciandaro M	Cabozantinib	17	All	Retrospective	35%	7.83 months (0.4–13.4)	12 months OS: 60%
Matthew T. Campbell	Cabozantinib	30	All	Retrospective	14.3%	8.6 months (6.1–14.7)	25.4 months (11.4–28.8)
De Giorgi U.	Nivolumab	35	All	Retrospective	19.3%	NR	NR
Koshkin Vadim S	Nivolumab	41	All	Retrospective	20%	3.5 months	Not reached

NR, not reported; OS, overall survival; PFS, progression free survival; ORR, objective response rate; N, number of patients.

and alteration in mitochondrial DNA, number and morphology could often been observed in this histotype suggesting that metabolic alteration occur very frequently (3-6).

- Translocation renal cell carcinoma (TRCC) is a specific tumour occurring generally in young patients. The most commonly alteration involves *TFE3* gene (Xp11.2) which encodes protein modulating transcription process. TFEB-amplified RCC is recently described entities and is associated to very aggressive disease. Of note, no alteration of VHL could be found in TRCC (3-6).
- Collecting duct carcinoma (CDC) is a tumour associated to metabolic shift and presents a strongly immunogenic behaviour due to the up-regulation of different genes involved in lymphocyte activity (3-6).

Table 2 Ongoing phase III and phase II studies on nccRCC

Study ID	Arm A	Arm B	Inclusion Criteria	Primary outcome	Other outcomes
NCT03091192 (SAVOIR), phase III	Savolitinib	Sunitinib	MET driven pRCC	PFS	OS/ORR
NCT02761057 (PAPMET), phase II	Cabozantinib	Sunitinib; Savolitinib; Crizotinib	pRCC	PFS	OS/ORR
NCT03354884 (BONSAI), phase II	Cabozantinib	–	CDC	ORR	PFS/OS
NCT03075423 (SUNNIFORECAST), phase II	Nivolumab, Ipilimumab	Sunitinib	nccRCC	12 months OS	PFS/ORR/OS
NCT02724878, phase II	Atezolizumab, Bevacizumab	–	nccRCC	ORR	PFS/OS
NCT02915783, phase II	Everolimus, Lenvatinib	–	nccRCC	ORR	PFS/OS
NCT02819596 (CALYPSO), phase II	Savolitinib, Durvalumab, Tremelimumab	–	nccRCC, ccRCC	Safety/ORR	PFS/OS
NCT03635892, phase II	Cabozantinib, Nivolumab	–	nccRCC	ORR	PFS/OS

nccRCC, non-clear cell renal cell carcinoma; pRCC, papillary renal cell carcinoma; MET, mesenchymal-epithelial transition receptor; CDC, collecting duct carcinoma; ORR, objective response rate; PFS, progression free survival; OS, overall survival.

- ❖ Renal medullary carcinoma (RMC) is a very uncommon diagnosis and alteration of genes regulating chromatin-remodelling complex (SMARCB1/INI1) have been described (3-7).

Molecular characterization of nccRCC has led to understand that these tumours have a very complex panel of altered genes and thus the development of new drugs for metastatic disease should be tailored for a specific genomic alterations or selected tumour histology.

Tailored trials are currently ongoing (*Table 2*). The MET inhibitor savolitinib has shown promising activity in pRCC with MET-driven mutations and a phase III trial (SAVOIR) comparing savolitinib to sunitinib in patients with MET-driven pRCC tumours is currently ongoing. The randomized phase II trial PAPMET is currently comparing a VEGFR, MET or VEGFR/MET (sunitinib, cabozantinib, Crizotinib, Volitinib) inhibition strategies in patients with pRCC unselected for MET. Other compounds are represented by PARP inhibitors in patients with hereditary leiomyomatosis and renal cell carcinoma syndrome; CDK4/6 inhibitors in tumors with CDKN2A loss and EZH2 inhibitors in tumours with INI1 (chromatin remodelling pathways mutations).

Despite tailored trials are surely a promising approach for the evaluation of new compounds in nccRCC it should not be forgotten that the results provided by these studies may require several years due to the low incidence of these tumours and thus the slow accrual of patients.

A revolution in the management of metastatic ccRCC is currently in progress and several new compounds have been approved in clinical practice (8).

As observed in "target therapy era" also recently registration clinical trials have excluded nccRCC from population on study. Therefore, once again our efforts should be spent to translate and evaluate the activity of these new compounds in patients with nccRCC.

Expanded access programs are a partial response to this need while real world experience studies may offer a large deal of data able to estimate the impact of these novel compounds in a population of nccRCC patients.

Cabozantinib is a tyrosine kinase inhibitor able to interfere with several altered pathways including: MET, AXL, VEGFR 2 and RET (9-13). In ccRCC it has been compared to everolimus in patients progressed to standard angiogenesis inhibitors (METEOR). In this population administration of cabozantinib leads to improved overall survival (21.4 versus 16.5 months; HR 0.66, 95% CI: 0.53–0.83), progression free survival (HR 0.51, 95% CI: 0.41–0.62) and objective response rate (17% *vs.* 3%) compared to everolimus (10,11). A randomized phase II studies (CABOSUN) has also compared cabozantinib to sunitinib in patients with intermediate or poor risk according to

IMDC criteria. Also in this population cabozantinib resulted in improved progression free survival (8.6 versus 5.3 months, HR 0.48, 95% CI: 0.31–0.74) and response rate (20% versus 9%) while no overall survival benefit emerged from this study (12,13).

Nowadays, cabozantinib is a recognized and effective treatment largely adopted in clinical practice and has shown clinical efficacy in patients who previously received immunotherapy (monotherapy), immunotherapy combination or angiogenesis inhibitors.

About nccRCC, evidences about the efficacy profiles of cabozantinib have been recently provided by Martínez Chanzá *et al.* Authors carried out a retrospective analysis of 112 nccRCC patients who received cabozantinib as first (20%), second (28%) or more advanced line (53%). The majority of tumours were pRCC (59%), TRCC (15%), ChRCC (9%), CDC (4%) and unclassified histology (13%). Treatment with cabozantinib was associated to a median progression free survival and overall survival of 7.0 (1.7–9.0 months) and 12.0 (9.2–17.2) months respectively. Overall 30 of 112 patients (27%, 95% CI: 19–36) achieved a RECIST response, while 47% achieved a stable disease as best response (14).

Of note response to treatment was observed regardless previous treatment received, bone metastases, Heng prognostic risk, histology (only unclassified RCC achieved a lowest rate of objective response: 13%) and presence of sarcomatoid features. Curiously, despite no difference in objective response rate have been observed in patients with/without sarcomatoid features, patients presenting sarcomatoid seems to show a lowest time of treatment failure (5.1, 95% CI: 2.8–6.2 versus 7.4, 95% CI: 4.6–11.0 months) and 12 months overall survival (25%, 95% CI: 8–47 versus 48%, 95% CI: 31–64). Of note, information about genomic assessment was obtained in 54 of 112 patients. CDKN2A was the most frequent alteration (22%) followed by MET (20%), TP53 (11%), FH (9%), SETD2, PTEN and NF2 (7% each one) (14). Response to treatment seemed to be not influenced by CDKN2A alteration while expression of MET resulted in higher response rate (4 of 10 patients with MET alteration achieved objective response, 40%) (14).

This study is for sure the largest evaluation of cabozantinib in nccRCC population and confirmed previous real-world data evaluating the use of cabozantinib in smaller population of nccRCC (15-19).

The inclusion of cabozantinib in clinical practice for this specific population is of particular importance as very few treatments are available for these patients. Sunitinib, temsirolimus and everolimus are the more evaluated compounds in nccRCC (*Table 1*). However, their clinical activity is modest in this population.

Immunotherapy, represented by immune-checkpoint inhibitors is another promising treatment strategy for patients with metastatic nccRCC. Two studies evaluated the impact of immunotherapy in small series of nccRCC (41 and 42 patients) (20,21). In these studies, Nivolumab was associated to an objective response rate of 19–20% and an overall survival of 12 months or more (20). Similar results have been achieved by a real-world experience carried out by De Giorgi *et al.* (21). In a phase Ia trial 70 patients with clear cell (n=63) and non clear cell (n=7) renal tumour progressed to mTOR and VEGF/VEGFR inhibitors received Atezolizumab (anti programmed death ligand 1) (22). This trial showed a favourable toxicity profile of the PD-L1 inhibitor with an interesting clinical efficacy (ORR 15%) especially in patients with poor prognostic features (ORR 22% in tumours with sarcomatoid features and high Fuhrman and ISUP grade). Among the seven patients with non-clear cell tumour (6 with papillary histology and 1 with unknown histology) no RECIST tumour responses have been observed (only 1 tumour response according to irRC) (22).

Cabozantinib may be attractive and effective drugs in patients with nccRCC. Nonetheless, more efforts should be spent for the detection of treatments able to improve survival of these patients.

Although several trials tailored for specific histology are currently ongoing other approaches may improve the management of nccRCC.

The development of shared databases as well as the development of network among research centres is a winning approach, which could partially help to overcome the physiological long time required for the results of perspective clinical trials.

Furthermore, the development of an upgraded data sets may provide reliable data, which may be used as comparator population in larger studies aimed to evaluate new compounds. This could be a possible approach to overcome problems related to the low incidence of these tumours.

Of course, these patients should be referred to reference centres and inclusion in clinical trials should be strongly encouraged due to the exiguity of demonstrated clinical effective treatments.

About new compounds under investigation, the combination between ipilimumab (an anti-CTLA-4 inhibitor) and Nivolumab is currently under investigation in patients with nccRCC. This randomized phase II trial comparing the combination to sunitinib (SUNNIFORACAST) is currently ongoing and open to all patients with nccRCC. A sequential approach (Nivolumab as single agent than associated to ipilimumab) is under investigation in UNISoN trial.

Also the combination between Atezolizumab and Bevacizumab (NCT02724878), lenvatinib everolimus (NCT02915783) is currently evaluating these approaches in patients with nccRCC. The combination between savolitinib and durvalumab is under evaluation in a phase I trial evaluating also savolitinib as mono-treatment, durvalumab as single treatment and the combination between tremelimumab and durvalumab (CALYPSO). The association between Cabozantinib and Nivolumab is also under evaluation (NCT03635892).

Expanded access programs will also offer the possibility to investigate the more recent combination (Avelumab-Axitinib, Pembrolizumab-Axitinib) in nccRCC patients.

In conclusion, we are assisting to a revolution in the management of metastatic renal cell carcinoma (23-25). Despite important progresses have been done for the molecular characterization and the development of new compounds, nccRCC still remains a disease associated to poorest outcomes and prognosis compared to ccRCC.

Cabozantinib may be an important treatment options for these patients as it seems be associated to clinical activity regardless histology.

The planning of nccRCC tailored trials is a critical issue for the development of new treatments.

The build of informatics databases, and shared networks may be a key step to acquire important data about management of these rare tumours.

Patients with diagnosis of metastatic nccRCC should be oriented in reference centres and inclusion in clinical trials should be strongly encouraged.

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Footnote

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