Tumori rari del rene: trattamento per stadio ed istologia

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Non-Clear Cell Renal Cell Carcinoma (nccRCC)

- **nccRCC represents a diverse group of tumours with varying genetic and histological characteristics[1,2]**
  - **Approximately 25% of RCC cases are nccRCC[1]**
- **Many nccRCC subtypes are:**
  - **Poorly characterised,**
  - **Some have only recently been described as discrete entities or emerging[2]**

1. Cohen HT et al. *N Engl J Med*. 2005;353:2477-2490. **2.** Srigley JR et al. *Mod Pathol*. 2009;22(suppl 2):S2-S23.

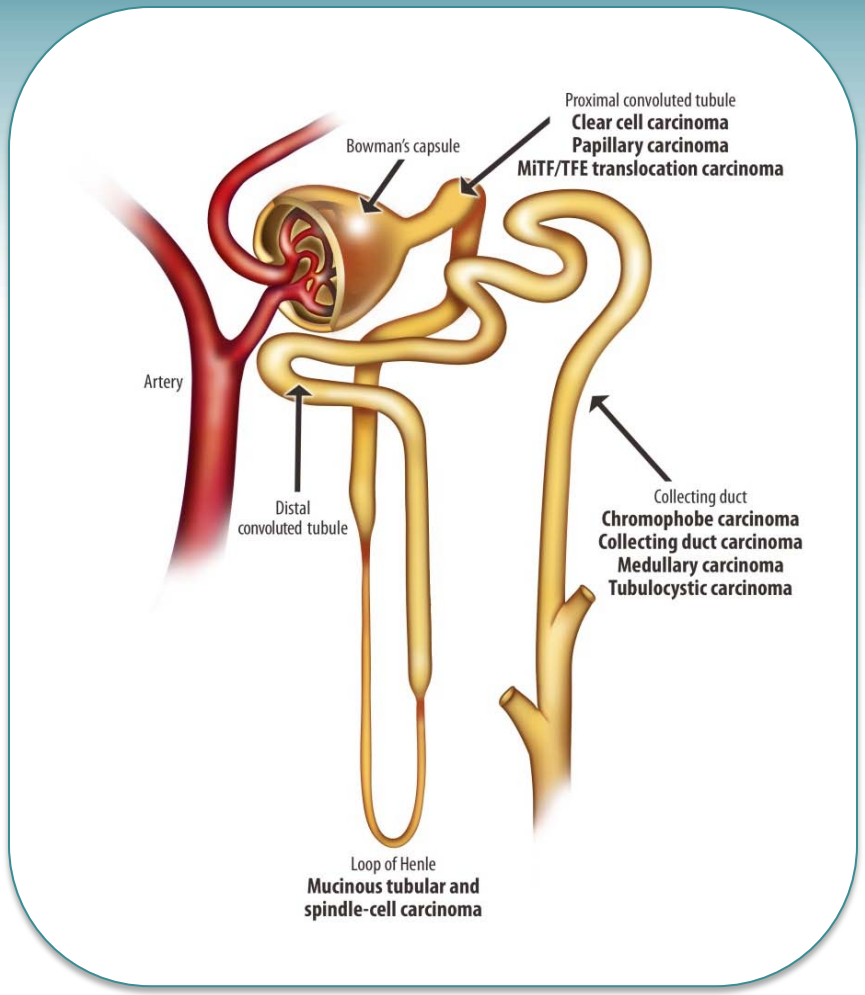
nccRCC Subtypes[1-4]

More Common

- Papillary RCC
- Chromophobe RCC

Less Common

- Collecting duct carcinoma
- Medullary carcinoma
- Mucinous tubular and spindle cell carcinoma
- Translocation RCC
- Post-neuroblastoma carcinoma
- Tubulocystic carcinoma
- Carcinoma associated with ESRD
- Follicular renal carcinoma
- Cystic RCC
- Oncocytic papillary RCC
- Leiomyomatous renal carcinoma



ESRD, end-stage renal disease

1. WHO. Classification of tumours, 2004. http://www.iarc.fr/en/publications/pdfs-online/pat-gen/index.php. **2.** Srigley JR et al. *Mod Pathol*. 2009;22(suppl 2):S2-S23. **3.** Oosterwijk E et al. *Eur Urol*. 2011;60:622-633. **4.** Lopez-Beltran A et al. *Eur Urol*. 2006;49:798-805.

nccRCC Treatment Options Are Limited

- **Efficacy and safety data are scarce**
  - **Patients usually excluded from pivotal trials[1]**
  - **No targeted therapies specifically approved for nccRCC**
- **Evidence-based treatment guidelines are limited[2,3,4]**
- **Clear guidance is lacking; optimal treatment strategy remains to be determined[5]**

1. Schrader AJ et al. *BJU Int*. 2008;101:1343-1345. **2.** NCCN. *Clinical Practice Guidelines in Oncology for Kidney Cancer*. V 2.2012. http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. **3.** Escudier B et al. *Ann Oncol*. 2010;21(suppl 5):v137-v139. **4.** Ljungberg B et al. *Eur Urol*. 2010;58:398-406. **5.** Singer EA et al. *Target Oncol*. 2010;5:119-129.

Available Data for Targeted Agents in nccRCC

- Efficacy and safety data are available mainly from:
  - Subgroup analysis of pivotal Temsirolimus RCT
  - Expanded Access Programmes (EAPs) of Sunitinib, Sorafenib and Everolimus
  - Few, retrospective, series
  - Sparse case-reports (for the rarest histotypes)

- Due to their intrinsic nature, all these data are biased and consequently have a low level of evidence

Subgroup Analysis of Patients With nccRCC From the Temsirolimus Trial

Study Design:
Phase III, randomised, open-label, exploratory analysis of patients with varying RCC histologies[1,2]

Patients:
- Treatment-naive, poor prognosis
- ccRCC: n = 339
- nccRCC: n = 73

Temsirolimus vs IFN

Primary end point
Median OS: months (95% CI):
ccRCC: 10.7 (8.5, 13.0) vs 8.2 (6.6, 10.4)

nccRCC: 11.6 (8.9, 14.5) vs 4.3 (3.2, 7.3)

Hazard Ratio for death
ccRCC: 0.82
nccRCC: 0.49

CI, confidence interval; HR, hazard ratio; IFN-α, interferon-α; OS, overall survival.

1. Hudes G et al. *N Engl J Med*. 2007;356:2271-2281. **2.** Dutcher JP et al. *Med Oncol*. 2009;26:202-209.

Subgroup Analysis of Everolimus EAP (REACT): Patients With nccRCC

Study Design:
Subgroup analysis of patients with nccRCC from REACT[1]

REACT: non-randomised, open-label EAP in mRCC patients who were intolerant of or had progressed on previous VEGFr-TKI therapy[2]

Patients:

Total population: N = 1367
ccRCC: n = 1283
nccRCC: n = 75

Best overall tumour response rates:
Total population
PR: 1.7%
SD: 51.6%

nccRCC
PR: 1.3%
SD: 49.3%

Safety profile: comparable in nccRCC and total populations

EAP, expanded-access program; PR, partial response; SD, stable disease.

1. Blank C et al. Presented at: European Multidisciplinary Cancer Congress; 23–27 September 2011; Stockholm, Sweden. 2. Grunwald V et al. *Eur J Cancer*. 2012;48:324-332 .

Subgroup Analysis of Sorafenib EAPs: Patients With nccRCC

Study Design: non-randomised, open-label expanded-access programme

Patients:

North American (NA)-ARCCS[1]
ccRCC: n = 2028
nccRCC: n = 202

European (EU)-ARCCS[2]
ccRCC: n = 909
nccRCC: n = 241

Median PFS (95% CI)

NA-ARCCS
Total Population: 24 weeks (22,25)
Excluding nccRCC: 24 weeks (22,25)

EU-ARCCS
Total population: 6.6 months (6.1,7.4)
nccRCC: ~ 3 m

- **DCR (12 weeks)**
  Total population: 78%
  nccRCC: ~50%

DCR, disease control rate (complete response + partial response + stable disease); PFS, progression-free survival.

1. Stadler WM et al. *Cancer*. 2010;116:1272-1280. **2.** Beck J et al. *Ann Oncol*. 2011;22:1812-1823.

Subgroup Analysis of Sunitinib EAP: Patients With nccRCC

Study Design:
Non-randomised, open-label expanded-access programme[1]

Patients:
ccRCC: n = 3758
nccRCC n = 588

Median PFS: months (95% CI)
Total population: 10.9 (10.3, 11.2)
nccRCC: 7.8 (6.3,8.3)

Median OS: months (95% CI)
Total population: 18.4 (17.4, 19.2)
nccRCC: 13.4 (10.7, 14.9)

Response*
Total population: **ORR** 17%, **SD**: 59%
nccRCC: **ORR** 11%; **SD** 57%

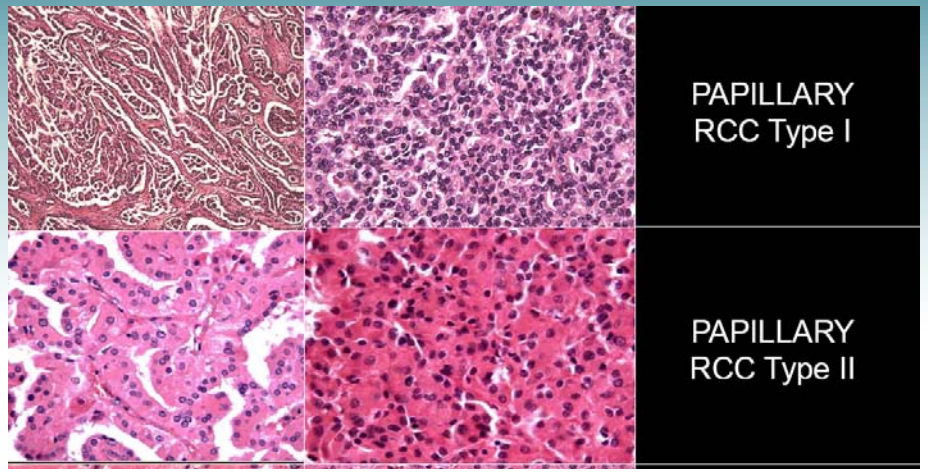
OR, objective response rate.
*Evaluable patients: total population: N = 3464; nccRCC: n = 437.

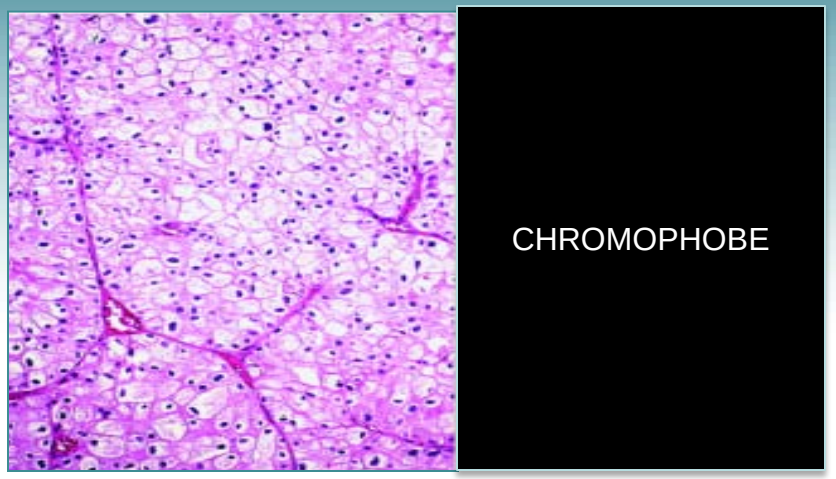
Gore ME, et al. *Lancet Oncol*. 2009;10:757-763.

Selected nccRCC Sybtypes

- Efficacy data and ongoing studies in specific nccRCC subtypes:
  - Papillary
  - Chromophobe
  - Translocation

Papillary and Chromophobe RCC





Type 1	Type 2
Trisomy of chromosomes 7 and 17	Chromosomal aberration, including loss of Y
Deregulated MET signaling pathway	**Defective genes encoding FH**
Rarely metastasize, generally good prognosis	High-grade, aggressive, tumours with a poor prognosis
Overall 5-year survival: 49% - 84% 7-year DFS: 92% (type1), 44% (type 2) Median OS in metastatic disease: 5.5 months	

Loss of heterozygosity in chromosomes 1, 2, 6, 10, 13,17, and 21, plus hypodiploidy

Prognosis generally good; long survival times and low mortality (around 10%)

5-year survival: 87.9%

Low rate of metastatic disease (2.9% - 4.9%)

Median survival in metastatic disease is 29 months

EAPs of Sorafenib or Sunitinib: patients with Papillary or Chromophobe RCC

Study Design:
Sunitinib or sorafenib in patients with papillary or chromophobe RCC[1]

Patients:
Papillary: n = 41
Chromophobe: n = 12

Papillary
Median PFS: 7.6 months
- Sunitinib 11.9 months vs sorafenib 5.1 months

Chromophobe
Median PFS: **10.6 months**
- Sunitinib 8.9 months vs sorafenib 27.5 months

Choueiri TK et al. *J Clin Oncol*. 2008;26:127-131.

Papillary RCC: Completed Clinical Trials

Erlotinib phase II study[1]

Patients: papillary RCC, n = 36

Foretinib (GSK1363089) phase II study[2,3]

Patients: Papillary RCC, n = 44

(two cohorts, different dosing schedules)

Erlotinib study:

PR rate: 11% (95% CI, 3%, 24%)
DCR: 64% (**PR**: n = 5; **SD**: n =24)
Estimated median survival: 27 months (95% CI: 13, 36)

Foretinib study:

Cohort 1: (n = 35) **PR**: n = 4; **SD**: n = 27
Cohort 2: (n = 9) **PR**: n = 2; **SD**: n = 7

1. Gordon MS et al. *J Clin Oncol*. 2009;27:5788-5793. **2.** Srinivasan R et al. *J Clin Oncol*. 2011;27(suppl 15):abstr 5103.
3. Clinicaltrials.gov identifier: NCT00726323.

Papillary RCC: Ongoing Clinical Trials (1)

Intervention	Study Design	End Points/ Preliminary Outcomes
Everolimus 10 mg/day	**RAPTOR[1]: Phase 2, multicentre (Europe), single-arm trial for advanced papillary RCC (type 1 and 2)** No prior systemic therapy for mRCC Target enrolment: N = 60	**Primary end point: PFS at 6 months** Secondary end points: DCR, ORR, duration of response, median PFS, safety
Sunitinib 50 mg/day, 4 weeks on, 2 weeks off	**SUPAP[2,3]: Phase 2, multicentre, single-arm trial for metastatic papillary RCC (type 1 and 2)** No prior systemic therapy for mRCC Target enrolment: N = 92	**Preliminary response rate is lower than with ccRCC[1]** **Type 1: n = 5 (3 evaluable)** **SD:** 3 patients **Type 2: n = 23** **PR:** 1 patient **SD:** 13 patients (4 patients, SD ≥12 weeks)

1. Clinicaltrials.gov identifier: NCT00688753. **2.** Ravaud A et al. *J Clin Oncol*. 2009;27(suppl 15):abstr 5146.
3. Clinicaltrials.gov identifier: NCT00541008.

Papillary RCC: Ongoing Clinical Trials (2)

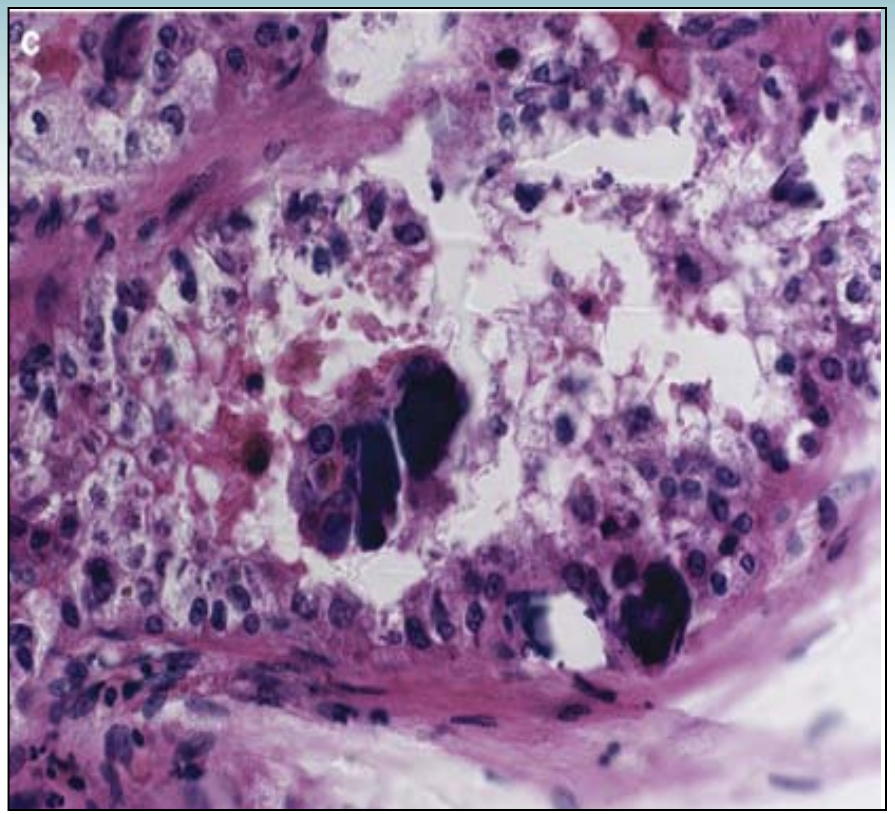
Intervention	Study Design	End Points
Bevacizumab 15 mg/kg every 3 weeks	**Phase 2, non-randomised, single-arm, open-label trial of papillary RCC[1]** No prior systemic therapy for mRCC Follow-up every 3 months for 1 year, then every 6 months for 3 years Target enrolment: N = 41	**Primary end point: PFS** Secondary end points: Response rate, OS
Bevacizumab every 3 weeks plus erlotinib daily in 28-day cycles	**Phase 2, non-randomised, single-arm, open-label trial for metastatic sporadic papillary RCC or metastatic HLRCC[2]** ≤2 prior VEGFr-TKIs (no prior bevacizumab) Target enrolment: N = 40	**Primary end point: ORR** Secondary end points: PFS, OS, duration of response, effect on CEC/CPS, effect on angiogenesis biomarkers

CEC = circulating endothelial cells; CPS = circulating progenitor cells; HLRCC = hereditary leiomyomatosis and renal cell carcinoma.

1. Clinicaltrials.gov identifier: NCT00601926. **2.** Clinicaltrials.gov identifier: NCT01130519.

Translocation RCC

- Constitutes <1% of all RCCs
- Common in children and young adults
- Mixed histology
- 90% of cases involve translocation of transcription factor E3 (TFE3) with different partner genes on Xp11.2
- Tumours are largely indolent
- Visceral or lymph node mets, 42%



Translocation RCC: Retrospective Analyses

Intervention	Patients	Outcomes	Conclusions
VEGFR-TKIs, bevacizumab, or ramucirumab[1]	**Advanced Xp11 translocation RCC** N = 15	**ORR: 20%** **PR: n = 3** **SD: n = 7** At median follow-up 19.1 months: • **PFS:** 7.1 months (95% CI: 1.7, 27.0) • **OS:** 14.3 months (95% CI: 2.7, NR)	**Clinical efficacy with VEGF-targeted therapy for XP11 translocation RCC**
VEGFR-TKIs, cytokines, or mTOR inhibitors[2]	**Metastatic Xp11.2 translocation RCC** N = 21	**First-line sunitinib vs cytokine:** **Median PFS:** months (95% CI) • 8.2 (2.6-14.7) vs 2.0 (0.8-3.3) (*P* = 0.003) **≥ Second-line:** **PR**: sunitinib, temsirolimus **SD**: sorafenib	**Targeted therapies show activity in patients with Xp11.2 translocation RCC**

1. Choueiri TK et al. *Cancer*. 2010;116:5219-5225. **2.** Malouf GG et al. *Ann Oncol*. 2010;21:1834-1838.

Conclusions

- nccRCCs are a clinically and genetically diverse group of tumours
- Evidence-based treatment recommendations are limited
- The VEGFR-TKIs sunitinib and sorafenib, the mTOR inhibitors temsirolimus and everolimus, the EGFR inhibitor erlotinib, and the novel dual VEGFRs and Met inhibitor Foretinib, have all shown some benefit in small trials, case series and EAPs
- Evidence from randomised studies is required before any agent can be adopted into routine clinical practice
- Enrolling patients in dedicated clinical trials is mandatory

Thank You for Your Kind Attention!!!

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