Survival data from patients with advanced or metastatic renal cell carcinoma in routine practice differ significantly compared to clinical trial data - Analyses from the German clinical RCC Registry

Goebell P.J.[1], Müller L.[2], Staehler M.[3], Nusch A.[4], Münz M.[5], Koska M.[5], Jänicke M.[5], Marschner N.[6] and the RCC Registry group

[1]Onkologische Schwerpunktpraxis Leer Emden, Leer, Germany, [2]Urologische Universitätsklinik im Waldkrankenhaus St. Marien, Erlangen, Germany, [3]Gemeinschaftspraxis für Hämatologie und Onkologie, Westerstede, Germany, [4]Praxis für Urologie, Chemnitz, Germany, [5]iOMEDICO, Freiburg, Germany, [6]Praxis für interdisziplinäre Onkologie & Hämatologie, Freiburg, Germany

Introduction:

The approval of targeted therapies for patients with advanced or metastatic renal cell carcinoma is based on (randomized) clinical trials that have strict criteria for eligibility to ensure high internal validity and patient homogeneity. “Real life” patients may not meet these criteria and are therefore often classified as ineligible for clinical trials. Clinical registries give insights into patient characteristics and their treatments and permit investigations of outcome of patients in routine practice. This may allow further investigating the pertinent question on overall survival differences between clinical trials compared to “real life”.

Methods:

The prospective, open, longitudinal, multicentre, clinical registry on renal cell carcinoma (RCC Registry, ClinicalTrials.gov registry: NCT00610012) recruits patients with advanced or metastatic RCC (mRCC) at the start of first-line treatment as administered by a network of German office-based medical oncologists and uro-oncologists. Starting in December 2007, 116 sites (currently 277 oncologists and uro-oncologists) are participating.

Patients receive standard treatments according to physician's choice. At time of enrolment, data on patient`s demography, tumour characteristics, clinical parameters, comorbidities and previous treatments are documented. During the course of therapy, all systemic treatments as well as outcome parameters including date of progression(s) and death are documented. Patients are followed until death or for a maximum of three years.

Automated plausibility and completeness checks with subsequently generated queries by the electronic data capture system ensure data reliability. In addition, the database is regularly checked for plausibility and completeness and study sites are contacted if required. Patients with histologically confirmed mRCC can be included if they have signed informed consent no longer than 1 year after the start of systemic 1st-line treatment. Outcome data, such as overall survival are analysed for all patients who signed informed consent no longer than six weeks after the start of 1st-line treatment. The restriction on patients who started treatment no long before consent is crucial to avoid an overestimation of outcome data.

In this analysis, we investigated the impact of common exclusion criteria in clinical trials on overall survival using a multivariate cox proportional hazards model. In addition, overall and progression free survival (OS/PFS) were estimated using the Kaplan-Meier method. Patients without progression/alive or lost to follow-up were censored with the last date of documented patients contact (interim analysis 15.05.2014).

Results:

“Trial ineligible” patients are more often affected by comorbidities compared to “potentially trial eligible” patients

At the time of this analysis, data of 732 prospectively documented patients were available to investigate criteria concerning trial eligibility. For 56% of patients at least one possible exclusion criteria was documented („trial ineligible“, Figure 1). These possible exclusion criteria were: low Karnofsky performance status (<80%), low haemoglobin (<lower limit of normal) or non-clear cell carcinoma. For 44% of patients none of these three common exclusion criteria were documented (“potentially trial eligible”, Figure 1).

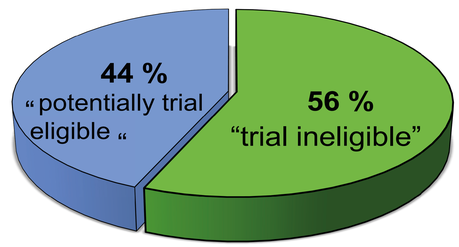

Figure 1: Patient population

For 412 patients (56%) at least one possible exclusion criteria was documented („trial ineligible“). These possible exclusion criteria were: Karnofsky performance status <80%, haemoglobin <lower limit of normal or non-clear cell carcinoma. For 320 patients (44%) none of these possible exclusion criteria were documented (“potentially trial eligible”).

Table 1 shows that “trial ineligible” patients are slightly older and more often affected by comorbidities than “potentially trial eligible” patients. Furthermore “trial ineligible” patients had less often undergone nephrectomy and only 10% are low risk patients, while more than 58% of “potentially trial eligible” patients have a low risk according to MSKCC risk score, i.e. are patients with a good prognosis. Median progression free survival is 5.6 months (95% CI 4.7-6.6 months) for the “trial ineligible” patients compared to 10.9 months (95% CI 9.7-13.4 months) for the “potentially trial eligible” patients.

Overall survival differs between “potentially trial eligible” and “trial ineligible” patients

In a multivariate analysis, all three common trial exclusion criteria had a significant negative impact on overall survival: Karnofsky performance status <80% (HR 1.745, 95% CI 1.366-2.230, p<.001), haemoglobin <lower limit of normal (HR 1.667, 95% CI 1.348-2.062, p<.001) and non-clear cell carcinoma (HR 1.427, 95% CI 1.123-1.812, p<.01).

At the time of this analysis, a total of 52% of patients had died. Median overall survival is 17.9 months (95% CI 15.6-20.6 months) since the start of first-line treatment (Table 1). Median overall survival of “potentially trial eligible” patients is 26.0 months (95% CI 22.1-31.5 months) whereas median overall survival of “trial ineligible” patients is 12.8 months (95% CI 10.2-16.0 months) (Table1, Figure 2).

Similar results were obtained when the sample was restricted to patients not treated with first-line mTOR: Median overall survival for “potentially trial eligible” patients is 26.2 months and for “trial ineligible” patients 15.4 months and median progression free survival is 10.9 months for “potentially trial eligible” patients compared to 6.6 months for “trial ineligible” patients.

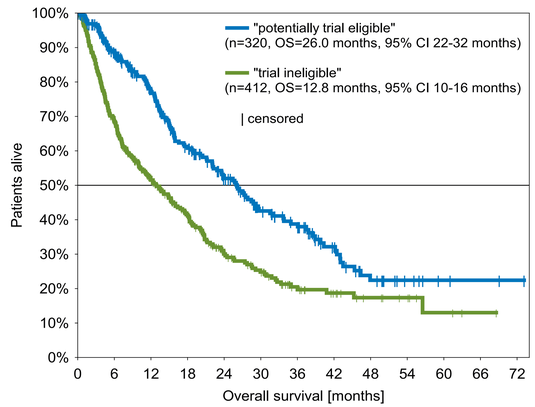

Figure 2: Overall survival since the start of first-line treatment

Number of patients who have been prospectively documented since the beginning of first-line treatment. The permanent black line marks the median.

Table 1: Patient characteristics, treatment and outcome

	Total	“Trial ineligible”	“Potentially trial eligible”
Number of patients N (%)	732	412 (56.3)	320 (43.7)
Female (%)	30.5	30.1	31.0
Age (years) [mean ± StD] [a]	68.0 [±10.0]	68.6 [±9.8]	67.3 [±10.2]
BMI [mean ± StD] [a]	27.0 [±4.8]	26.4 [±4.4]	27.7 [±5.1]
CCI (0-24) [mean ± StD] [a,b]	0.7 [±1.4]	0.9 [±1,5]	0.5 [±1.1]
MSKCC risk factors [a]			
[0] low risk (%)	31.0	10.0	58.1
[1-2] intermediate risk (%)	44.1	64.3	18.1
[3-5] high risk (%)	8.6	15.3	-
unknown (%)	16.3	10.4	23.8
Nephrectomy (%) [c]	74.2	70.2	79.5
Karnofsky performance status <80% [a]			
yes (%)	20.8	36.9	-
no (%)	72.0	58.0	90.0
unknown (%)	7.2	5.1	10.0
Haemoglobin < lower limit of normal [a]			
yes (%)	40.0	71.1	-
no (%)	56.3	28.2	92.5
unknown (%)	3.7	0.7	7.5
Calcium > upper limit of normal [a]			
yes (%)	4.2	5.1	3.1
no (%)	85.9	88.6	82.5
unknown (%)	9.8	6.3	14.4
Histology [c]			
Clear cell carcinoma (%)	70.1	55.6	88.8
Non-clear cell carcinoma (%)	20.5	36.4	-
unknown (%)	9.4	8.0	11.3
First-line treatment strategy			
TKI (%)	67.9	63.6	73.4
mTOR (%)	15.4	20.9	8.4
Other (%)	16.7	15.5	18.1
PFS [median in months (95% CI)]	7.9 (6.8-9.2)	5.6 (4.7-6.6)	10.9 (9.7-13.4)
Censored cases (%)	37.7	33.4	43.3
OS [median in month (95% CI)]	17.9 (15.6-20.6)	12.8 (10.2-16.0)	26.0 (22.1-31.5)
Censored cases (%)	47.8	42.0	55.3

[a] At start of first-line treatment.
[b] The Charlson Comorbidity Index (CCI) indicates to what extent patients are affected by comorbidities at the start of first-line therapy (Quan et al., 2011).
[c] At primary diagnosis

Conclusion:

Our data show that more than 50% of patients in German routine practice would be ineligible for participation in a clinical trial. Their overall survival is inferior compared to “potentially trial eligible” patients. Similar findings were reported from 19 international cancer centres for mRCC patients treated with first-line VEGF therapy (Heng et al., 2014). Survival times reported in clinical trials cannot be directly transferred to patients excluded from these trials. However, these patients are treated in routine practice. Physicians should be aware of these differences when discussing treatment options and outcome data with individual patients.

In cooperation with:

AKS Arbeitskreis klinische Studien e.V.

BUND DER UROLOGEN e.G.

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Acknowledgement
The RCC Registry group thanks all participating patients, physicians and study teams.
Project idea, design, management and analysis: iOMEDICO AG.
The RCC registry is conducted in cooperation with the Arbeitskreis Klinische Studien in onkologischen und hämatologischen Praxen e.V. and the Bund der Urologen e.G.

Disclosures
No relevant conflicts of interest to declare

EAU Congress, Madrid 2015

Abstract ID Number: AM15-0858
New Number: 6