Do we need new high-risk criteria for surgically treated renal cancer patients to improve the outcome of future clinical trials in the adjuvant setting? Results of a comprehensive analysis based on the multicenter CORONA database

I. Wolff [a,*,1], M. May [b,1], B. Hoschke [a], R. Zigeuner [c], L. Cindolo [d], G. Hutterer [c], L. Schips [d], O. De Cobelli [e], B. Rocco [f], C. De Nunzio [g], A. Tubaro [g], I. Coman [h], B. Feciche [h], M. Truss [i], O. Dalpiaz [c], R.S. Figenshau [j], K. Madison [j], M. Sanchez-Chapado [k], M.D.C. Santiago Martin [k], L. Salzano [l], G. Lotrecchiano [l], S.F. Shariat [m], M. Hohenfellner [n], R. Waidelich [o], C. Stief [o], K. Miller [p], S. Pahernik [n,1], S. Brookman-May [o,1], Members of the CORONA Project and the European Association of Urology (EAU) Young Academic Urologists (YAU) Renal Cancer Group

[a] *Carl-Thiem-Klinikum Cottbus, Department of Urology, Cottbus, Germany*
[b] *St. Elisabeth-Klinikum Straubing, Department of Urology, Straubing, Germany*
[c] *Medizinische Universität zu Graz, Department of Urology, Graz, Austria*
[d] *Pio Da Pietrelcina Hospital, Department of Urology, Vasto, Italy*
[e] *European Institute of Oncology, Division of Urology, Milan, Italy*
[f] *Università degli Studi di Milano, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Department of Urology, Milan, Italy*
[g] *Faculty of Health Sciences, University "La Sapienza", Ospedale Sant'Andrea, Department of Urology, Rome, Italy*
[h] *Clinical Municipal Hospital, Department of Urology, Cluj-Napoca, Romania*
[i] *Klinikum Dortmund, Department of Urology, Dortmund, Germany*
[j] *Washington University School of Medicine, Department of Surgery, Division of Urologic Surgery, St. Louis, Washington, USA*
[k] *Hospital Universitario Principe de Asturias, Alcala de Henares, Department of Urology, Madrid, Spain*
[l] *G. Rummo Hospital, Department of Urology, Benevento, Italy*
[m] *Medical University of Vienna, Department of Urology, Vienna, Austria*
[n] *Ruprecht-Karls-Universität Heidelberg, Department of Urology, Heidelberg, Germany*
[o] *Ludwig-Maximilians-Universität München, Department of Urology, Munich, Germany*
[p] *Charite-Universitätsmedizin Berlin, Department of Urology, Berlin, Ge*

Abstract

Background: Since there is still an unmet need for potent adjuvant strategies for renal cancer patients with high progression risk after surgery, several targeted therapies are currently evaluated in this setting. We analyzed whether inclusion criteria of contemporary trials (ARISER, ASSURE, SORCE, EVEREST, PROTECT, S-TRAC, ATLAS) correctly identify high-risk patients.
Methods: The study group comprised 8873 patients of the international CORONA-database after surgery for non-metastatic renal cancer without any adjuvant treatment. Patients were divided into potentially eligible high-risk and assumable low-risk patients who didn't meet inclusion criteria of contemporary adjuvant clinical trials. The ability of various inclusion criteria for disease-free survival (DFS) prediction was evaluated by Harrell's c-index.
Results: During a median follow-up of 53 months 15.2% of patients experienced recurrence (5-year-DFS 84%). By application of trial inclusion criteria, 24% (S-TRAC) to 47% (SORCE) of patients would have been eligible for enrollment. Actual recurrence rates of eligible patients ranged between 29% (SORCE) and 37% (S-TRAC) opposed to <10% in excluded patients. Highest Hazard Ratio for selection criteria was proven for the SORCE-trial (HR 6.42; $p < 0.001$), while ASSURE and EVEREST reached the highest c-index for DFS prediction (both 0.73). In a separate multivariate Cox-model, two risk-groups were identified with a maximum difference in 5-year-DFS (94% vs. 61%).
Conclusion: Results of contemporary adjuvant clinical trials will not be comparable as inclusion criteria differ significantly. Risk assessment according to our model might improve patient selection in clinical trials by defining a high-risk group (28% of all patients) with a 5-year-recurrence rate of almost 40%.

Keywords: Renal cell cancer; Nephrectomy; Disease recurrence; Adjuvant therapy; Phase-3-trials; Targeted agents

Introduction

Renal cell carcinoma (RCC) constitutes about 2e3% of all malignant tumors in adults.1 Staging according to TNM- classification, Fuhrman grade, histological subtype, and tu- mor size are known to be the strongest predictors of onco- logical outcome in RCC patients after surgical treatment.1e3 Depending on the individual risk profile, 10e50% of patients will experience disease recurrence or progression.1e3 Therefore, there is a clear rationale for adjuvant treatment in high-risk RCC patients after surgery.4e7
Several placebo controlled studies evaluating the effi- cacy of various adjuvant treatment approaches have been conducted, but until now, no compound has demonstrated a significant benefit with regard to disease-free survival (DFS).5e9 Only for the adjuvant autologous tumor cell vac- cine Reniale® a significant improvement in 5-year-DFS has been shown (77.4% vs. 67.8%; p 0.0204), however, despite these encouraging results, this immunotherapy has not been approved by health authorities due to limitations in study concept and trial conduction.10
Over the past years, several targeted agents have been approved in the setting of metastatic RCC.8 In an effort to transpose these substances into the adjuvant setting, several large phase 3 trials have been initiated. Currently, results of seven trials in the adjuvant setting are awaited, some of which are still enrolling patients, while others have finished recruitment already. Initial results of two trials are currently available. Adjuvant treatment with the CA-IX antibody Gir- entuximab, which was tested in the ARISER trial, did not result in a significant endpoint improvement.11 Also in the ASSURE trial both Sunitinib and Sorafenib failed to

improve DFS and overall survival as compared to placebo.12 Results of all other trials in the adjuvant setting are currently lacking and will have to be awaited, before any final conclu- sions can be drawn (Table 1).
Considering expected side effects, it seems essential to identify patients at high risk for recurrence or progression and to exclude patients at low-risk in order to minimize overtreatment when trials for adjuvant approaches are de- signed. Ideally, inclusion criteria should be adopted from validated prognostic models that reliably estimate the risk of postoperative treatment failure.13 However, inclusion criteria of contemporary trials conducted in the adjuvant setting differ significantly, which allows the conclusion that we still miss a consistent definition of risk profiles (Table 1).
The aim of this study was to analyze the discriminative power of inclusion and exclusion criteria, which are currently applied in all ongoing clinical phase 3 trials, for the prediction of disease recurrence in the adjuvant setting.

Patients and methods

Patients and study design

Clinical and histopathological data were collated from a database of 8837 patients who underwent nephron-sparing surgery (NSS) or radical nephrectomy (RN) with curative intent for unilateral sporadic RCC (clear cell, papillary or chromophobe histological subtype) without distant metas- tases (M0). Patients were treated in one of 12 centers of the international CORONA (Collaborative Research on Renal Neoplasms Association) project. All patients repre- sent consecutive cases in the participating centers, although not all centers covered the whole study period from 1992 to 2010 (nineteen years).
Preoperative staging included computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and imaging of the chest (X-ray in two planes or CT/MRI). Bone scan or cranial CT was only performed when indi- cated by symptoms or in case of locally advanced tumors. Patients didn't receive any neoadjuvant or adjuvant treat- ment. The following clinical parameters were recorded: date of surgery, patient's age at the time of surgery, gender, surgical procedure (RN vs. NSS, and extent of surgery

(regional lymph node dissection/rLND yes vs. no). The indication for simultaneous resection of the ipsilateral adre- nal gland or for rLND was set in case of suspect lesions on preoperative imaging or based on individual intraoperative surgeon's decision. All surgical specimens were worked up according to pathological standard procedures and histo- pathologically evaluated by experienced uro-pathologists at each institution. Pathological staging (pTN) was adapted to the 2009 classification system.14 Differentiation of tu- mors was assessed according to Fuhrman nuclear grade.15 Histological subtype was determined according to the Hei- delberg classification, while only clear cell, papillary and chromophobe subtypes were included into further ana- lyses.16 Presence of tumor necrosis was defined as micro- scopic detection of coagulative necrosis with a threshold of at least 10% of tumor tissue and characterized by ho- mogenous clusters of degenerated or necrotic cells; infor- mation on this feature was available in 72.1% of the study patients (n 6400).17 In addition, maximum tumor diameter was assessed.
Based on these histopathological findings, patients were identified, who met the inclusion criteria of the following large contemporary adjuvant trials: ARISER, ASSURE, SORCE, EVEREST, PROTECT, S-TRAC and ATLAS (http://clinicaltrials.gov) (Table 1).

Oncologic outcome

Oncological follow-up was performed based on perti- nent guidelines with individual modifications by each participating center. Disease recurrence was defined as sys- temic relapse (distant metastasis and/or non-regional lymph node metastasis) and/or local recurrence (ipsilateral adrenal metastasis or regional lymph node metastasis). Isolated local relapse within the remaining part of the kidney after NSS or in the renal bed after RN was considered a pure operative therapy failure and not recorded as recurrence in order to achieve a consistent definition of systemic relapse. Information on time of recurrence was established by contacting patients' attending physician. Disease recurrence built the endpoint of this study. The database was finally updated with follow-up data in June 2012 and was closed thereafter.

Statistical analysis

Continuous variables are displayed with medians and in-
terquartile ranges (IQR). DFS was estimated according to the Kaplan-Meier-method. Differences in DFS between pa- tients who would have been included and those who would have been excluded from current clinical trials based on their clinical and pathological features were analyzed by log-rank-testing. Predictive accuracy (PA) for predicting postoperative recurrence in patients potentially eligible vs. patients not eligible for these trials were evaluated by assessing c-indices according to Harrell.18 In doing so, a c-index of 0.5 is equivalent to coin tossing whereas a c-in- dex of 1 represents an optimal discrimination between pa- tients experiencing recurrence and those with disease-free survival. Hazard Ratios (HR) and c-indices were calculated using univariate and multivariate analyses adjusted for age, sex, and type of surgery. By application of an additional multivariate Cox regression model, a potential independent impact of pT- the study endpoint DFS was tested. Subsequently, these criteria were evaluated according to the results of the Cox model aiming at improving the discriminative ability of the dichotomization based on inclusion and exclusion criteria.
Data were evaluated using R statistical package (v.2.12.2) and SPSS 19.0 (SPSS Inc. Chicago, IL, USA). Reported p-values are two-sided with the statistical significance level set at p :S 0.05.

Results

Clinical and histopathological criteria of 8873 study pa- tients undergoing surgery for non-metastatic RCC are dis- played in Table 2. By application of inclusion criteria of the seven adjuvant clinical trials, between 24% (S-TRAC) and 47% (SORCE) of these patients would have been eligible for enrollment into these trials (Table 3).
Median follow-up (calculated from date of surgery) of patients without disease recurrence at last contact was 52.8 months (IQR: 23e98). 15.2% (1351/8873) of patients experienced tumor recurrence during follow-up; accordant DFS rates were 94%, 88%, 84%, and 78% after 1, 3, 5, and 10 years, respectively. The risk of recurrence varied be- tween eligible patients for the adjuvant trials, while it was lower than 10% (4.9e9.8%) in patients who did not comply with high-risk definitions and who were therefore assigned to the low-risk group (Table 3).
Table 3 also shows DFS rates after five years for RCC patients eligible for enrollment based on respective inclu- sion criteria of each trial and for those patients not meeting these criteria. The best HR in the univariate Cox model could be demonstrated when selection criteria of the SORCE-trial were applied (HR 6.42; $p < 0.001$), while the highest PA for DFS prediction was reached by ASSURE and EVEREST (both 73.2%, Table 3). After ad- justing the model for age, sex, and surgical approach, PA of the different selection criteria was improved to rates be- tween 71.9% (S-TRAC) and 75% (ASSURE, EVEREST) (Table 3).

Based on the results of a separate multivariate Cox model including pT-stage, pN-stage, Fuhrman grade, and tumor diameter, two distinct groups with a maximum dif- ference in DFS could be separated: a low-risk group (n 6384; 71.9%) consisting of patients with RCC staged pT1-2 or pT3a with a tumor diameter 7 cm, pN0/pNx, Fuhrman grade 1e2 vs. a high-risk group (n 2489; 28.1%)

including patients with tumors featuring either stage pT3a with a diameter >7 cm, stages pT3b, pN stage or Fuhrman grade 3e4 (data not shown). These groups showed DFS rates of 94% and 61% after 5 years, respectively ($p < 0.001$) (Table 3, Fig. 1). By application of these selection criteria for definition of a high and a low risk profile, considerably higher HRs for DFS predic- tion were achieved in comparison to risk grouping as applied in currently ongoing clinical trials (HRunivariate: 6.59; HRmultivariate: 5.85; Table 3). Corresponding Pas reached 72.4% (univariate) and 75.8% (multivariate;Table 3).

Discussion

To our knowledge, this is the first large multicenter study analyzing the predictive power of different inclusion criteria which are applied in contemporary clinical trials

in the adjuvant treatment setting for RCC patients. In the present study, 15.2% of all 8873 patients experienced dis- ease recurrence during follow-up, which is comparable to findings in other pertinent studies (10e50%).3,13,19 Inclu- sion criteria for patient eligibility differed considerably among the analyzed clinical trials, which will make com- parison of results of these trials quite challenging as already discussed by different authors.6,19

In the present multicenter database, the proportion of patients considered eligible for an adjuvant clinical trial based on the inclusion criteria of each trial varied signifi- cantly between these trials, from 24% for S-TRAC up to 47% in SORCE. Of patients potentially suitable for inclu- sion, a fraction of 29% (SORCE) to 37% (S-TRAC) expe- rienced recurrence. This emphasizes again the urgent need for an adjuvant treatment in these high-risk patients. On the other hand, less than 10% of patients who did not meet the inclusion criteria and who were therefore consid- ered low-risk developed recurrence after surgery. Based on this low number of recurrent cases, it sounds reasonable to exclude these patients from adjuvant trials and adjuvant treatment in general in order to avoid associated side effects and overtreatment. Notably, despite different inclu- sion criteria, all trials showed a similar and relatively high PA between 68.3% and 73.2%.

Our results concerning the predictive power of inclusion criteria applied in contemporary clinical trials in the adju- vant setting are consistent with published literature on this topic. Kim et al. reported on a single-center cohort of 1363 patients after surgery for non-metastatic RCC and noted recurrence in 23% of patients.19 Consistent with our findings, 23% (S-TRAC) to 47% (SORCE) of their pa- tients met the inclusion criteria of the different contempo- rary trials. Among eligible patients, 43% (SORCE) - 59% (S-TRAC) developed disease progression, while only 6e18% of patients not meeting the inclusion criteria expe- rienced recurrence. This slightly higher proportion of pa- tients experiencing recurrence may be attributable to different definitions of recurrence. In the present study, pa- tients with an isolated local relapse were considered local surgical failure and therefore not recognized as progressive disease while Kim et al. recorded both local recurrence and distant metastasis as progressive disease.

Concordant with the analysis by Kim et al., interpreta- tion of the present study may be hampered by the retrospec- tive study design. In contrast to the single-center study by Kim et al., our multicenter study is limited by the lack of standardization for diagnostic procedures, therapy, and follow-up despite application of current guidelines. No cen- tral pathology review was performed as this would have been virtually impossible for more than 8800 patients. As already mentioned, information on tumor necrosis was available in 6400 of all study patients only (72.1%) so that inclusion criteria of the SORCE-trial could just be evaluated based on an accordingly smaller patient cohort. Since patients with other than clear-cell histology were not considered for analysis of ARISER, PROTECT, S- TRAC and ATLAS, the final study group for testing the in- clusion criteria of these trials comprised of 7112 patients (80.2% of all patients).

PA of selection criteria could be slightly improved to rates between 71.9% (S-TRAC) and 75% (ASSURE, EVEREST) by adjusting the model for patients' age, gender, and surgical approach (NSS vs. RN). Applying a separate multivariate Cox model including pT-stage, lymph node involvement, Fuhrman grade, and tumor size, PA of dichotomization in two distinctive risk groups could be further increased to 72.4% (univariate) and 75.8% (multi- variate), respectively. According to this model, a low-risk group of patients with tumors staged pT1-2 or pT3a with a tumor diameter 7 cm, pN0/pNx, and Fuhrman grade 1e2 (n 6384; 71.9%) was clearly separated from a high-risk group of patients featuring RCC either staged pT3a with a diameter >7 cm, stages > pT3b, pNþ or Fuhr- man grade 3e4 (n ¼ 2489; 28.1%). These groups showed DFS rates of 94% and 61% after 5 years, respectively. The need for inclusion of a 7 cm tumor diameter cut-off at stage pT3a in order to achieve the best possible PA for prognosis confirms findings recently published by the CORONA group on a different patient population.20 As new therapeu- tic options such as immune checkpoint inhibition have already shown promising results in patients with metastatic RCC, these approaches may also be evaluated in the adju- vant setting in the near future.6 Incorporation of the high- risk definition as proposed based on the present study re- sults for assessment of patient eligibility in upcoming clin- ical trials focusing on immune checkpoint blockade and other approaches in the adjuvant setting should be consid- ered in order to reliably identify patients at high risk for recurrence after surgery and thus avoid overtreatment.

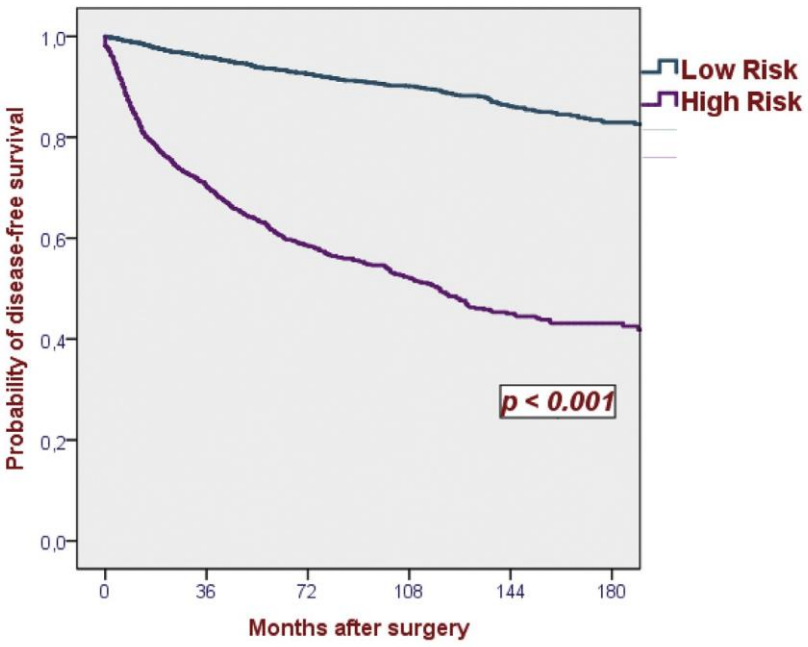
References

1. Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol 2015;67(5):913–24.
2. Meskawi M, Sun M, Trinh QD, et al. A review of integrated staging systems for renal cell carcinoma. Eur Urol 2012;62(2):303–14.
3. Karakiewicz PI, Suardi N, Capitanio U, et al. Conditional survival pre- dictions after nephrectomy for renal cell carcinoma. J Urol 2009; 182(6):2607–12.
4. Brookman-May S, May M, Gilfrich C, Wieland WF, Burger M. Can vaccination or tyrosine kinase inhibitor therapy play a role in the adju- vant treatment of renal cell carcinoma? Expert Rev Anticancer Ther 2010;10(6):813–23.
5. Janowitz T, Welsh SJ, Zaki K, Mulders P, Eisen T. Adjuvant therapy in renal cell carcinoma-past, present, and future. Semin Oncol 2013; 40(4):482–91.
6. Pal SK, Haas NB. Adjuvant therapy for renal cell carcinoma: past, pre- sent, and future. Oncologist 2014;19(8):851–9.
7. Tobert CM, Uzzo RG, Wood CG, Lane BR. Adjuvant and neoadjuvant therapy for renal cell carcinoma: a survey of the society of urologic oncology. Urol Oncol 2013;31(7):1316–20.
8. renal cell carcinoma: are all strategies equally negative? Potential im- plications for trial design with targeted agents. Clin Genitourin Cancer 2013;11(4):471–6.
9. Brookman-May S, Langenhuijsen JF, Volpe A, et al. Management of localized and locally advanced renal tumors. A contemporary review of current treatment options. Minerva Med 2013;104(3): 237–59.
10. Jocham D, Richter A, Hoffmann L, et al. Adjuvant autologous renal tumor cell vaccine and risk of tumor progression in patients with renal-cell carcinoma after radical nephrectomy: phase III, randomised controlled trial. Lancet 2004;363(9409):594–9.
11. Belldegrun AS, Chamie K, Kloepfer P, et al. ARISER: a randomized double blind phase III study to evaluate adjuvant cG250 treatment versus placebo in patients with high-risk ccRCCdresults and implica- tions for adjuvant clinical trials. J Clin Oncol 2013;31. (suppl 15; abstr 4507).
12. Haas NB, Manoala J, Uzzo RG, et al. Initial results from ASSURE (E2805): adjuvant sorafenib or sunitinib for unfavorable renal carci- noma, an ECOG-ACRIN-led, NCTN phase III trial. J Clin Oncol 2015;33. (suppl 7; abstr 403).
13. Karakiewicz PI, Briganti A, Chun FK, et al. Multi-institutional valida- tion of a new renal cancer-specific survival nomogram. J Clin Oncol 2007;25(11):1316–22.
14. Greene FL, Gospodarowicz M, Wittekend C, et al. American Joint Committee on Cancer (AJCC) staging manual. 7th ed. Philadelphia, PA: Springer; 2009.
15. Fuhrman S, Lasky LC, Limas L. Prognostic significance of morpho- logic parameters in renal cell carcinoma. Am J Surg Pathol 1982;6: 655–63.
16. Kovacs G, Akhtar M, Beckwith BJ, et al. The Heidelberg classification of renal cell tumors. J Pathol 1997;183(2):131–3.
17. Pflanz S, Brookman-Amissah S, Roigas J, Kendel F, Hoschke B, May M. Impact of macroscopic tumor necrosis to predict survival of patients with surgically resected renal cell carcinoma. Scand J Urol Nephrol 2008;42(6):507–13.
18. Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15: 361–87.
19. Kim SP, Crispen PL, Thompson RH, et al. Assessment of the patho- logic inclusion criteria from contemporary adjuvant clinical trials for predicting disease progression after nephrectomy for renal cell carci- noma. Cancer 2012;118(18):4412–20.
20. Brookman-May SD, May M, Wolff I, et al. Evaluation of the prog- nostic significance of perirenal fat invasion and tumor size in patients with pT1-pT3a localized renal cell carcinoma in a comprehensive multicenter study of the CORONA project. Can we further improve prognostic discrimination for patients with stage pT3a tumors? Eur Urol 2015;67(5):943–51.

Table 1
Summary of the seven contemporary clinical, placebo-controlled, double-blind multicenter trials on adjuvant treatment with targeted agents for high-risk renal cell carcinoma patients after initial surgery (http://clinicaltrials.gov), [ECOG-PS for all studies 0e1].

a) Acronym b) NCT Trial-Number c) Status	a) Number of study patients (n) b) Study start date c) End of study (scheduled)	a) Primary study endpoint b) Interventional arm(s)[#]	Exclusion criteria
a) ARISER b) NCT00087022 c) trial completed, no final publication	a) 864 b) July 2004 c) October 2012	a) DFS and OS b) Girentuximab, weekly for 24 weeks (intravenously)	1. non-ccRCC 2. pT1-2, pN0/x, FG1-2
a) ASSURE b) NCT00326898 c) active, recruiting completed	a) 1923 b) April 2006 c) April 2016	a) DFS b) 9 cycles of Sunitinib daily (4 weeks on, 2 weeks off) or Sorafinib twice daily for 1 year (orally)	1. Duct-Bellini-RCC* 2. pT1a, pN0/x, FG_{all} 3. pT1b, pN0/x, FG1-2
a) SORCE b) NCT00492258 c) trial completed, not published	a) 1656 b) June 2007 c) December 2012	a) DFS b) Sorafinib twice daily for 1 year, followed by 2 years of placebo, or: Sorafinib twice daily for 3 years (orally)	1. pT1a, pNþ, FG1-2, TN- 2. pT1a, pN0/x, FG1-3, TNþ 3. pT1b, pN0/x, FG1-2, TN-
a) EVEREST (S0931) b) NCT01120249 c) active, recruiting	a) 1218 b) April 2011 c) October 2021	a) DFS b) 9 cycles of Everolimus daily for 6 weeks (orally)	1. Duct-Bellini-RCC* 2. pT1a, pN0/x, FG_{all} 3. pT1b, pN0/x, FG1-2
a) PROTECT b) NCT01235962 c) active, recruiting completed	a) 1500 b) November 2010 c) April 2019	a) DFS b) Pazopanib daily for 1 year (orally)	1. non-ccRCC 2. pT1, pN0/x, FG_{all} 3. pT2, pN0/x, FG1-2
a) S-TRAC b) NCT00375674 c) active, recruiting	a) 735 b) August 2007 c) April 2016	a) DFS b) Sunitinib daily (4 weeks on, 2 weeks off) for 1 year (orally)	1. non-ccRCC 2. pT1-2, pN0/x, FG_{all} 3. pT3, pN0/x, FG1
a) ATLAS b) NCT01599754 c) active, recruiting	a) 700 b) April 2012 c) May 2019	a) DFS b) Axitinib twice daily for 3 years (orally)	1. non-ccRCC 2. pT1, pN0/x, FG_{all}

Legend: DFS, disease-free survival; OS, overall survival; [#]all studies (two- and three-arm trials) were placebo controlled; *exclusion of rare non-ccRCC (other than cc, papillary and chromophobe subtype); RCC, renal cell carcinoma; cc, clear cell; FG_{all}, all Fuhrman grades; ECOG-PS, Eastern Cooperative Oncology Group-Performance Score; TN, tumor necrosis.



Number of patients at risk	0 months	36 months	72 months	108 months	144 months	180 months
Low Risk	6384	4176	2365	1434	725	301
High Risk	2489	1149	548	316	159	78

Figure 1. Disease-free survival (DFS) of 8873 study patients with renal cell carcinoma after surgery (all M0) separated in groups according to the calculation of the multivariate Cox-model (pT1-2 or pT3a with tumor diameter :S7 cm, pN0/x, G1-2 [Low Risk] vs. pT3a with tumor diameter >7 cm or > pT3b or pNþ or G3-4 [High Risk]).

Table 3
Disease-free survival (DFS) of 8873 study patients with renal cell carcinoma after surgery (all M0) based on different inclusion criteria of seven contemporary clinical trials on adjuvant treatment with targeted agents according to the calculation of the multivariate Cox-model.

Patients included for analysis of each trial and proportion of patients matching inclusion criteria	Recurrence n/n (%)	DFS after 5 years, p-value	HR (95%CI), p-value PA (DFS) [univariate model]	HR (95%CI), p-Wert PA (DFS) [adjusted for age, sex, and surgical approach]
ARISER (n ▯ 7112; ccRCC only)		*p < 0.001*	5.461 (4.79e6.22)	4.775 (4.17e5.47)
No (n ¼ 4533; 63.7%)	315/4533 (6.9%)	93.4%	*p < 0.001*	*p < 0.001*
Yes (n ¼ 2579; 36.3%)	844/2579 (32.7%)	66.7%	PA: 71.8%	PA: 74.2%
ASSURE (n ▯ 8873)		*p < 0.001*	6.123 (5.39e6.95)	5.562 (4.84e6.39)
No (n ¼ 5555; 62.6%)	313/5555 (5.6%)	94.6%	*p < 0.001*	*p < 0.001*
Yes (n¼ 3318; 37.4%)	1038/3318 (31.3%)	68.3%	PA: 73.2%	PA: 75.0%
SORCE (n ▯ 6400; data on TN required)		*p < 0.001*	6.419 (5.44e7.57)	5.431 (4.56e6.47)
No (n ¼ 3408; 53.2%)	167/3408 (4.9%)	95.8%	*p < 0.001*	*p < 0.001*
Yes (n ¼ 2992; 46.8%)	865/2992 (28.9%)	71.7%	PA: 72.1%	PA: 74.8%
EVEREST (n ▯ 8873)		*p < 0.001*	6.123 (5.39e6.95)	5.562 (4.84e6.39)
No (n ¼ 5555; 62.6%)	313/5555 (5.6%)	94.6%	*p < 0.001*	*p < 0.001*
Yes (n ¼ 3318; 37.4%)	1038/3318 (31.3%)	68.3%	PA: 73.2%	PA: 75.0%
PROTECT (n ▯ 7112; ccRCC only)		*p < 0.001*	4.945 (4.38e5.58)	4.311 (3.79e4.91)
No (n ¼ 5038; 70.8%)	415/5038 (8.2%)	91.9%	*p < 0.001*	*p < 0.001*
Yes (n ¼ 2074; 29.2%)	744/2074 (35.9%)	64.2%	PA: 71.0%	PA: 73.5%
S-TRAC (n ▯ 7112; ccRCC only)		*p < 0.001*	4.490 (4.00e5.04)	3.832 (3.39e4.33)
No (n ¼ 5433; 76.4%)	532/5433 (9.8%)	90.5%	*p < 0.001*	*p < 0.001*
Yes (n ¼ 1679; 23.6%)	627/1679 (37.3%)	61.8%	PA: 68.3%	PA: 71.9%
ATLAS (n ▯ 7112; ccRCC only)		*p < 0.001*	4.877 (4.29e5.54)	4.300 (3.75e4.93)
No (n ¼ 4628; 65.1%)	342/4628 (7.4%)	92.8%	*p < 0.001*	*p < 0.001*
Yes (n ¼ 2484; 34.9%)	817/2484 (32.9%)	67.2%	PA: 71.3%	PA: 73.5%
Risk-groups based on our model (n ▯ 8873)		*p < 0.001*	6.594 (5.89e7.39)	5.849 (5.20e6.58)
pT1-2 or pT3a with TMD :S7 cm and pN0/x and G1-2 (n ¼ 6384; 71.9%)	459/6384 (7.2%)	93.5%	*p < 0.001*	*p < 0.001*
pT3a with TMD >7 cm or pT3b-4 or pNþ or G3-4 (n ¼ 2489; 28.1%)	892/2489 (35.8%)	61.4%	PA: 72.4%	PA: 75.8%

Legend: DFS, disease-free survival; PA, predictive accuracy; ccRCC, clear cell renal cell carcinoma; TN, tumor necrosis; TMD, histopathologic tumor diameter; 95%CI, 95% confidence interval.