Supplementary

Table 1 Characteristics of the clinical trials included in the meta-analysis. References of included studies refer to the Bibliography of the manuscript. Abbreviations: cc = clear cell; ncc = non clear cell; DFS = disease free survival; OS = overall survival; UISS = University of California Los Angeles Integrated Staging System; SSIGN = stage, size, grade and necrosis score; Exp. = experimental.

Study	Stage	cc (n%)/ ncc (n%)		Risk staging system	Treatment Experimental/control		Duration of treatment	Dose reduction		Patients n treatment group / n tot	Median DFS (yr)	Median OS (yr)	Most common adverse events (≥ grade 3)
ASSURE (Haas) (16)	pT1b G3−4 N0 (or pNx where clinically N0) M0, to any T any G N + (fully resected) M0	79%	21%	UISS	• Sunitinib 50 mg once daily, 4-weeks on/2-weeks off • Sorafenib 400 mg twice-daily Starting doses amended for the first one or two cycles • Sunitinib: 37,5 mg once daily • Sorafenib 400 mg once daily	Placebo	54 weeks	Started at reduced doses: • Sunitinib/placebo: 380/1294 patients • Sorafenib/placebo: 378/1296	Exp. Sunitinib	647/1943	5.8	Not reached	Hypertension (17%) Hand-foot syndrome (15%) Rash (2%)
									Exp. Sorafenib	649/1943	6.1	Not reached	Hypertension (16%) Hand-foot syndrome (33%) Rash (15%)
									Control	647/1943	6.6	Not reached	Hypertension (4%) Hand-foot syndrome (1%) Rash (1%)
S-TRAC (Ravaud) (12)	T3 or T4 and N0 or Nx M0, or any T and N+ M0	100%	0%	UISS	Sunitinib 50 mg once daily, 4-weeks on/2-weeks off	Placebo	1 year	Dose reduction to 37,5 mg once daily in the sunitinib group: 34.3%	Exp.	309/615	6.8	Not reached	Palmar-plantar erythrodysesthesia (16%) Hypertension (7.8%) Neutropenia (7.5%)
									Control	306/615	5.6	Not reached	Palmar-plantar erythrodysesthesia (0.3%) Hypertension (1.3%)
PROTECT (Motzer) (14)	pT2 G3-4 N0 M0, pT3-T4 any G N0 M0, or any pT any G N1 M0	100%	0%	SSIGN	Pazopanib 800 mg once daily Starting dose amended to 600 mg once daily	Placebo	1 year	Dose reduction in pazopanib 800 mg: 60% Dose reduction in pazopanib 600 mg: 51%	Exp.	800 mg: 198/1538 600 mg: 571/1538 ITT_{ALL} (800+600 mg): 769/1538	ITT_{ALL} not reported	Not reported	Hypertension (25%) Increased ALT (16%) Diarrhea (7%)
									Control	769/1538	ITT_{ALL} not reported	Not reported	Hypertension (7%) Increased ALT (1%) Diarrhea (1%)
ATLAS (Gross-Goupil) (17)	≥pT2 and/or N+ M0, any Fuhrman grade, ECOG PS 0/1	100%	0%	TNM and Fuhrman grade	Axitinib 5 mg twice-daily	Placebo	3 years	Dose reduction in the axitinib group: 56%	Exp.	363/724	Not reported	Not mature	Treatment-related grade 3-4 adverse events (49%)
									Control	361/724	Not reported	Not mature	Treatment-related grade 3-4 adverse events (12%)
SORCE (Eisen) (18)	Leibovich score (3-11)	84%	16%	Leibovich score (3-11)	Sorafenib 1 year or sorafenib 3 year (400 mg daily starting dose. 400 mg bd maximum dose)	Placebo	1 or 3 years	400 mg daily starting dose. Increase of dose up to 800 mg in patients without or with low toxicity. 200 mg daily minimum dose	Exp 1 Y	642/1711	5 Y DFS 67%	10 Y OS 69%	Hypertension (26%) Hand-foot skin reaction (24%) Rash (7%)
									Control	430/1711	5 Y DFS 67%	10 Y OS 70%	Hypertension (20%)
									Exp 3 y	639/1711	5 Y DFS 65%	10 Y OS 69%	Hypertension (24%) Hand-foot skin reaction (24%) Rash (10%)
									Control	430/1711	5 Y DFS 67%	10 Y OS 70%	Hypertension (20%)

METHODS

Search strategies

All phase III clinical trials published until 1 October 2019, evaluating clinical role of tyrosine kinase inhibitors in RCC were retrieved by three different authors (VDN,VM and FM). Keywords used for searching on Pubmed/Medline, Cochrane library, and Scopus, were: *''Adjuvant''* OR *''post operative''* OR *''peri operative''* AND *''sunitinib''* OR *''pazopanib''* OR *''sorafenib''* OR *''pazopanib''* OR *''axitinib''* OR *''everolimus''* OR *''temsirolimus''* OR *''cabozantinib''* OR *''lenvatinib''* OR *''tivozanib''* OR *''TKI''* OR *''tyrosine kinase inhibitors''* AND *''Renal Cell Carcinoma''* OR *''RCC''* OR *''renal tumours''* OR *'' renal carcinoma''*; only papers published in peer-reviewed journals, and written in English language, were considered. Furthermore, proceedings of the main International Oncological and Urological meetings (American Society of Clinical Oncology, European Society of Medical Oncology, American Association for Cancer Research, European Association of Urology, and American Urological Association), were also searched from 2005 onwards for relevant abstracts. When more than one report was available describing results of the same trial, the most recent information (corresponding to a longer follow-up and/or a higher number of patients) was considered in the analysis. Studies selected from first analysis were then restricted to clinical trials and then reviewed by three authors (VDN, VM and FM) separately in three different times.

Aims of the meta-analysis

Aims of the meta-analysis were:

(i) To evaluate the correlation between adjuvant tyrosine kinase inhibitors and Overall Survival (OS) in all patients. For this aim, phase III randomized clinical trials evaluating TKIs impact on OS were eligible.

(ii) To evaluate the correlation between adjuvant tyrosine kinase inhibitors and Disease Free Survival (DFS) in all patients. For this aim, phase III randomized clinical trials evaluating TKIs impact on DFS were eligible.

Data extraction and synthesis

The following data were extracted for each publication: (a) study; (b) stage; (c) percentages of patients with clear cell or non clear cells tumours; (d) risk staging system adopted; (e) experimental treatment and comparator arm; (f) dosage of experimental drugs; (g) percentage of patients who experienced dose reduction; (h) number of patients; (i) OS and DFS outcome expressed as HR for patients treated with tyrosine kinase inhibitors compared to placebo comparator arm.

In addiction we collected all risk staging system adopted specifying which were the categories of risk considered and the percentage of patients in each risk categories.

Three separate Authors (VDN, VM and FM) conducted the search and identification independently in three different times.

Statistical design

Co-primary endpoints of the meta-analysis were OS and DFS in all patients.

Meta-analysis was performed using the Review Manager (RevMan 5.3) software. Summary measure was HR with 95% CI for OS and DFS. HRs selected for analysis were adjusted for the maximum number of covariates. We applied the inverse variance technique for the meta-analysis of the HRs.. Statistical heterogeneity between studies was examined using the χ^2 test and the I^2 statistic.