Supplementary Table 1 Patient demographics and baseline characteristics.

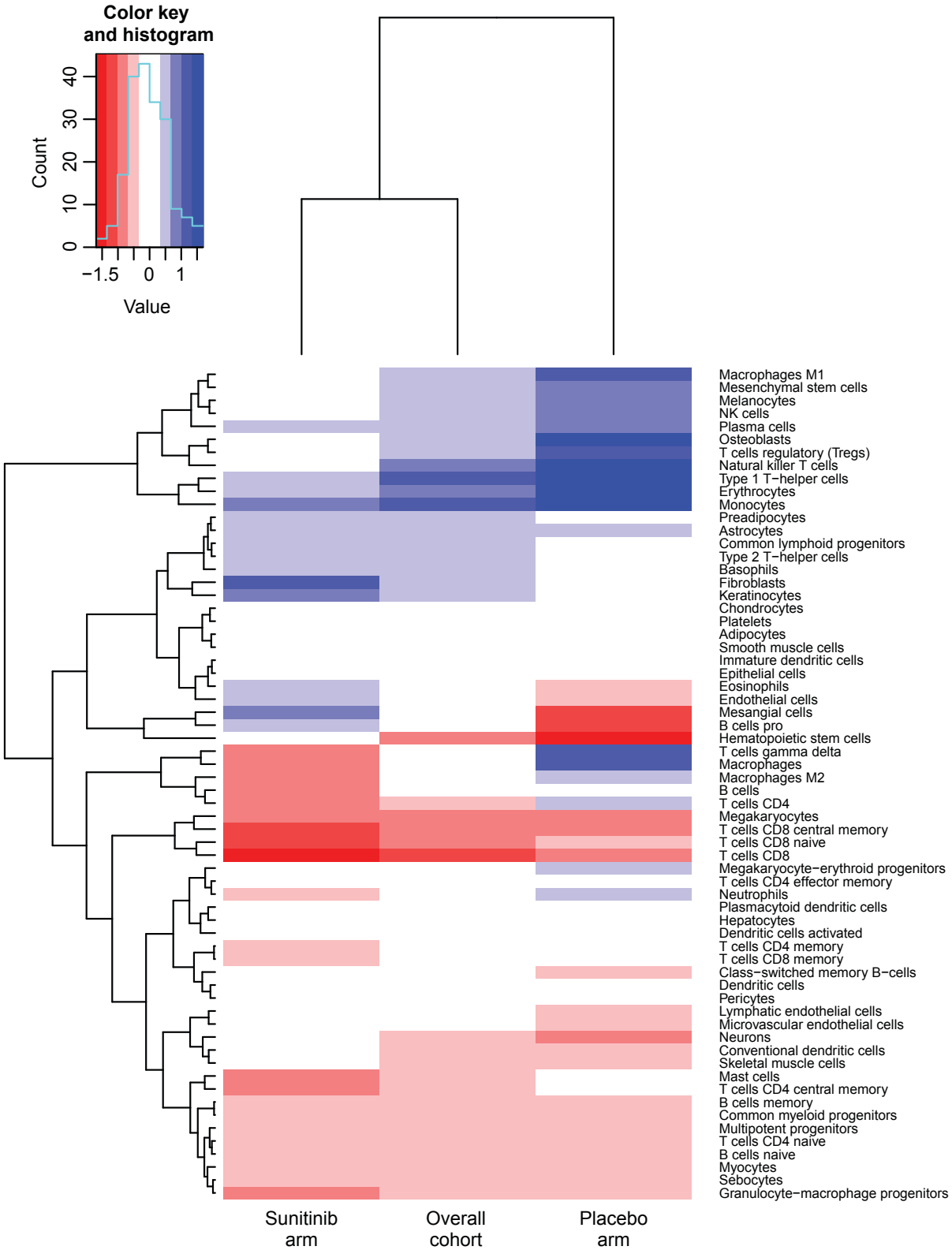
	WES Population			GES Population		
Variables, n (%)	Sunitinib n=91	Placebo n=80	P-value	Sunitinib n=72	Placebo n=61	P-value
Age, years						
<65	67 (73.6)	52 (65.0)	0.2461	53 (73.6)	43 (70.5)	0.7025
≥65	24 (26.4)	28 (35.0)		19 (26.4)	18 (29.5)	
Race						
White	76 (83.5)	70 (87.5)	0.3160	58 (80.6)	53 (86.9)	0.3002
Black	0	1 (1.3)		0	1 (1.6)	
Asian	13 (14.3)	6 (7.5)		12 (16.7)	5 (8.2)	
Other	2 (2.2)	3 (3.8)		2 (2.8)	2 (3.3)	
ECOG PS						
0	65 (71.4)	59 (73.8)	1.000	50 (69.4)	40 (65.6)	0.8497
1	24 (26.4)	21 (26.3)		20 (27.8)	20 (32.8)	
2	1 (1.1)	0		1 (1.4)	0	
NR	1 (1.1)	0		1 (1.4)	1 (1.6)	
UISS high-risk group						
T3 low[a]	28 (30.8)	25 (31.3)	0.9623	22 (30.6)	20 (32.8)	0.3884
T3 high[b]	56 (61.5)	48 (60.0)		47 (65.3)	36 (59.0)	
T4 N0 or NX, M0[c]	2 (2.2)	1 (1.3)		1 (1.4)	0	
Any T, N1-2, M0[c]	5 (5.5)	6 (7.5)		2 (2.8)	5 (8.2)	

[a] N0 or NX, M0, any Fuhrman's grade and ECOG PS 0 or T3 N0 or NX, M0, Fuhrman's grade 1 and ECOG PS ≥1.
[b] N0 or NX, M0, Fuhrman's grade ≥2 and ECOG PS ≥1.
[c] Any Furhman's grade and any ECOG PS.
Race, height, and weight were recorded at each site during screening. Race was investigator-reported in the study Clinical Research Form.
A two-sided log-rank test was used to obtain the P-values; no adjustments were made for multiple comparisons
ECOG PS=Eastern Cooperative Oncology Group performance status; GES=gene expression signatures; M=metastasis; N=node; NR=not reported; NX=nearby lymph nodes cannot be assessed due to lack of information; T=tumor; UISS=University of California-Los Angeles Integrated Staging System; WES=whole exome signatures

Supplementary Table 2 Complete listing of each institutional review board or independent ethics committee, listed by country

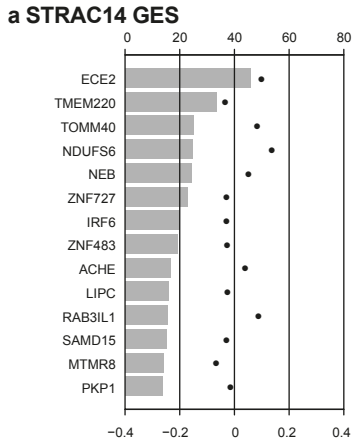
Czech Republic
Multicentricka eticka komise Fakultni nemocnice Motol V Uvalu 84 Praha 5, CZECH REPUBLIC 150 06
France
Centre Hospitalier Universitaire Pontchaillou Comite de protection des personnes "Ouest V" Pavillon Clemenceau Rennes cedex, FRANCE 35033
Germany
Ethik-Kommission der Medizinischen Fakultaet der Ludwig-Maximilians Universitaet Muenchen Pettenkoferstr. 8a Muenchen, GERMANY 80336
Greece
National Ethics Committee 284 Mesogeion Avenue Cholargos Athens, ATTIKI GREECE 15562
Ireland
SJH/AMNCH Research Ethic Committee FDVH Annex Adelaide and Meath Hospital Tallaght Dublin, IRELAND 24
Italy
Comitato Etico A.O.R.N. A. Cardarelli A.O.R.N. Santobono-Pausilipon Via Antonio Cardarelli, 9 Napoli, ITALY 80131
Comitato Etico Centrale IRCCS Lombardia, Fondazione IRCCS Instituto Nazionale dei Tumori di Milano Via Venezian, 1 Milano, ITALY 20133
Comitato Etico Delle provincie di Chieti e Pescara ASL di Lanciano -Vasto- Chieti Via dei Vestini 29B Chieti Scalo, ITALY 66013
Comitato Etico Indipendente dell'Azienda Ospedaliero Universitaria, Policlinico Sant' Orsola Padiglione 3 Via Albertoni, 15Malpighi di Bologna Bologna, ITALY 40138
Comitato Etico Val Padana Viale Concordia, 1 Cremona, ITALY 26100
Poland
Komisja Bioetyczna Wojskowego Instytutu Medycznego ul. Szaserow 128 Warszawa, POLAND 04-141
Slovakia
Fakultna nemocnica s poliklinikou Eticka komisia Vojtecha Spanyola 43 Zilina, SLOVAKIA 012 07
Eticka komisia, Univerzitna nemocnica Bratislava Pracovisko: Nemocnica akademika L. Derera Limbova 5 Bratislava, SLOVAKIA 833 05
Spain
Comite Etico de Investigacion Clinica Hospital Clinico i Provincial de Barcelona C/ VILLARROEL, 170 BARCELONA, BARCELONA SPAIN 8036
Switzerland
Kantonale Ethikkommission Bern (KEK) Postfach 56 Bern, SWITZERLAND 3010
Taiwan
Institutional Review Board of Taipei Veterans General Hospital 201, Sec. 2. Shih-Pai Road Taipei, TAIWAN 112
United States
The University of North Carolina at Chapel Hill Medical School Bldg 52 105 Mason Farm Road Office of Human Research Ethics CB 7097 Chapel Hill, NC UNITED STATES 27599-7097
Western Institutional Review Board 3535 Seventh Ave SW Olympia, WA UNITED STATES 98502

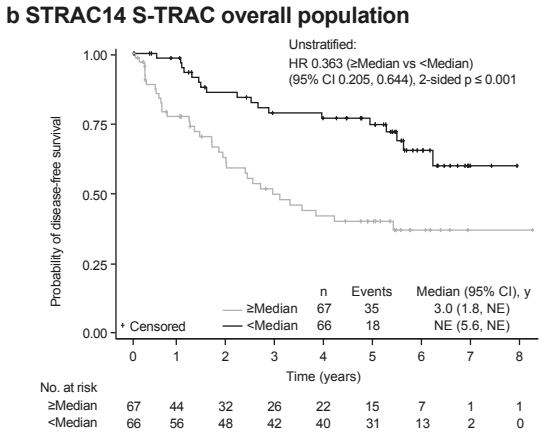
Supplementary Fig. 1 Complete profile of cell types significantly associated with DFS . Longer DFS (red), shorter DFS (blue), and non-significant (white) are shown. Each cell type score (xCell) was stratified by >median or ≤median for the overall cohort, sunitinib arm, or placebo arm. The log2(HR) was clustered in a heatmap.

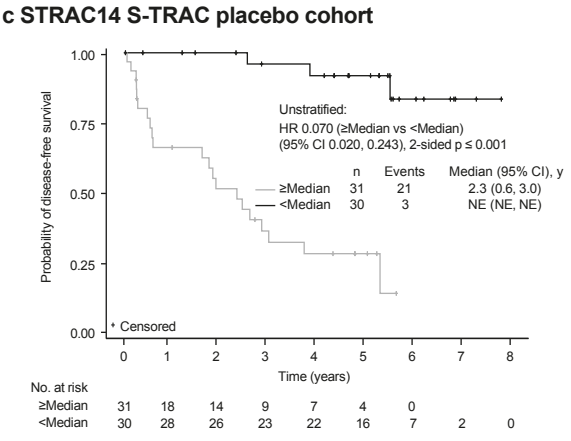


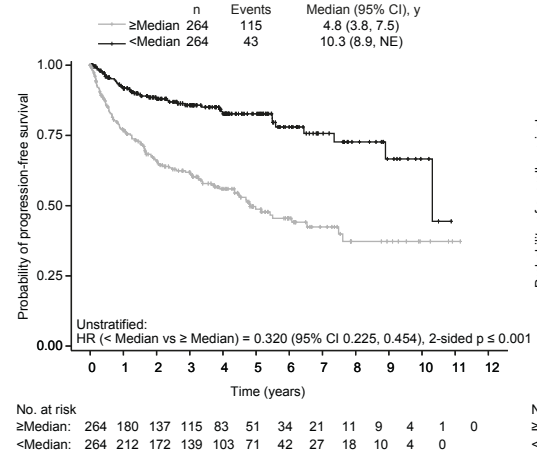
DFS=disease-free survival; HR=hazard ratio. For significant and non-significant cell types for both arms and overall cohort, data are available in raw data file FigureS1_cell_types_assoc_with_DFS/data.tsv

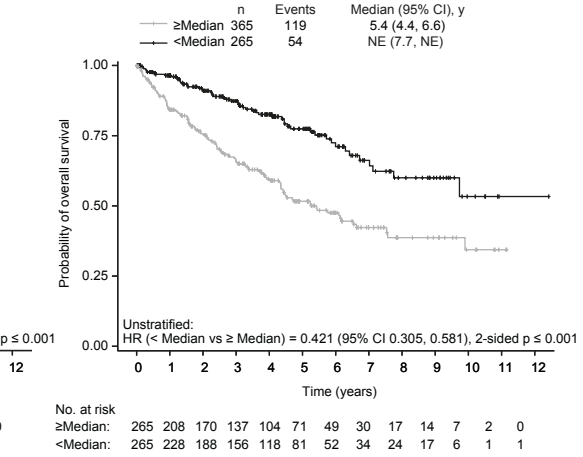
Supplementary Fig. 2 Identification of new transcriptomic STRAC14 signature associated with high risk of recurrence and poor prognosis. (**a**) Discovery of the STRAC14 GES according to bootstrapping frequency [derived from the placebo-treated S-TRAC trial population]. Kaplan–Meier plot of (**b**) differential DFS probability by STRAC14 in the S-TRAC overall population and (**c**) by treatment arm. Kaplan-Meier plot of (**d**) differential PFS probability, and (**e**) and differential OS probability by STRAC14 in TCGA data set and differential PFS probability by STRAC14 in the JAVELIN Renal 101 (**f**) overall data set and (**g**) by treatment arm. For panels 2b-g, a two-sided log-rank test was used and no adjustments were made for multiple comparisons.

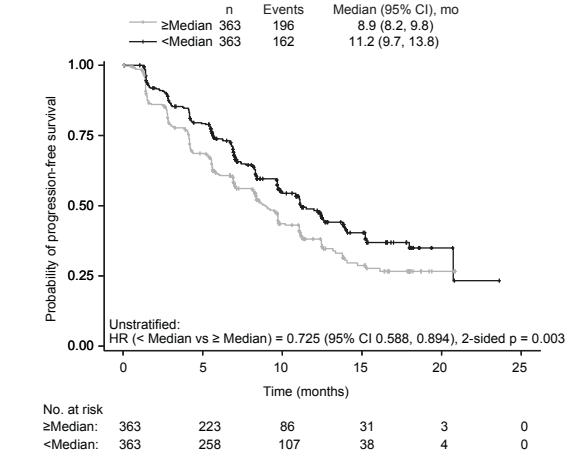


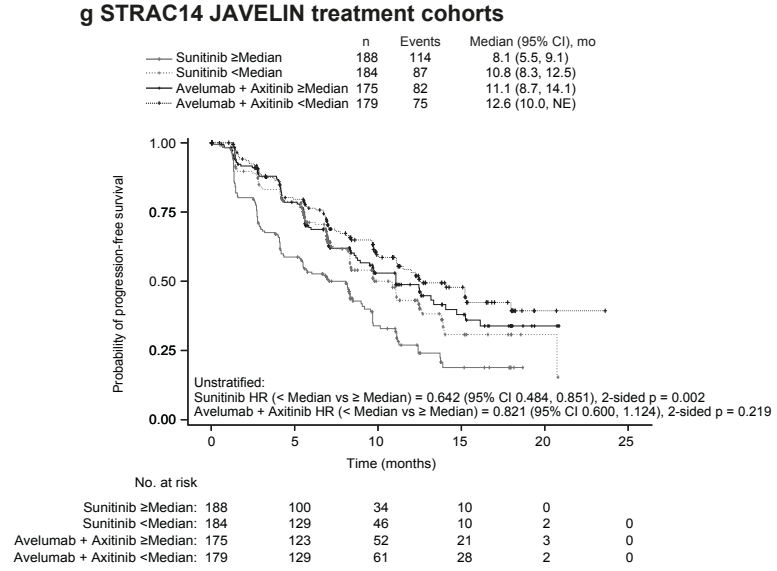






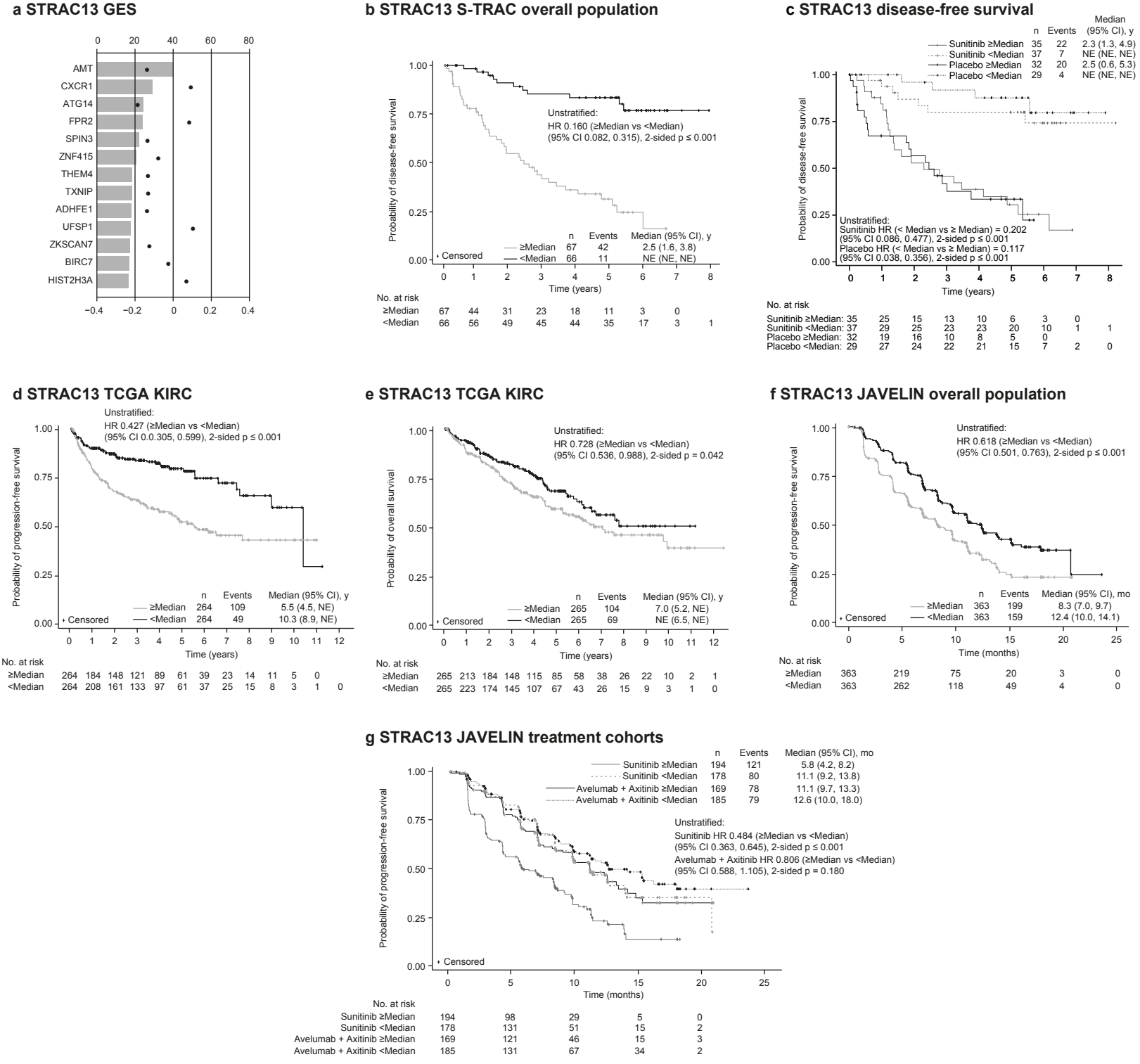






ACHE=acetylcholinesterase; CI=confidence interval; DFS=disease-free survival; ECE2=endothelin converting enzyme 2; HR=hazard ratio; IRF6= interferon regulatory factor 6; LIPC=lipase C (hepatic type); MTMR8=myotubularin related protein 8; NE=not estimable; NEB=nebulin; NDUFS6= NADH:ubiquinone oxidoreductase subunit S6; OS=overall survival; PFS=progression-free survival; PKP1=plakophilin 1; RAB3IL1=RAB3A interacting protein like 1; SAMD15=sterile alpha motif domain containing 15; STRAC14=gene expression signature of 14 genes; TCGA KIRC=The Cancer Genome Atlas Kidney Renal Clear Cell Carcinoma; TMEM220=transmembrane protein 220; TOMM40=translocase of outer mitochondrial membrane 40; ZNF483=zinc finger protein 483; ZNF727=zinc finger protein 727

Supplementary Fig. 3 Identification of new transcriptomic STRAC13 signature associated with high risk of recurrence and poor prognosis. (**a**) Discovery of the STRAC13 GES according to bootstrapping frequency [derived from entire S-TRAC trial population]. Kaplan–Meier plot of (**b**) differential DFS probability by STRAC13 in the S-TRAC overall population and (**c**) by treatment arm. Kaplan-Meier plot of (**d**) differential PFS probability, and (**e**) and differential OS probability by STRAC13 in TCGA data set and differential PFS probability by STRAC13 in the JAVELIN Renal 101 (**f**) overall data set and (**g**) by treatment arm. For panels 3b-g, a two-sided log-rank test was used and no adjustments were made for multiple comparisons.



ADHFE1=alcohol dehydrogenase iron containing 1; AMT=aminomethyltransferase; ATG14=autophagy-related 14; BIRC7=baculoviral IAP repeat containing 7; CI=confidence interval; DFS=disease-free survival; CXCR1=C-X-C motif chemokine receptor 1; DFS=disease-free survival; FPR2=formyl peptide receptor 2; GES=gene expression signature; HIST2H3A=histone cluster 2 H3A; HR=hazard ratio; NE=not estimable; OS=overall survival; PFS=progression-free survival; SPIN3=spindlin family member 3; STRAC13=gene expression signature of 13 genes; TCGA KIRC=The Cancer Genome Atlas Kidney Renal Clear Cell Carcinoma; THEM4=thioesterase