# Phase 3 trial of adjuvant sunitinib in patients with high-risk renal cell carcinoma: comprehensive tumor genomic and transcriptomic analyses

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# Disclosures

I am an employee of Pfizer
I own Pfizer stocks

The Pfizer drug, sunitinib, discussed in this presentation is presented in the context of a clinical trial and is not approved by the EMA for this indication.

# Background

- With increasing number of patients diagnosed with renal cell carcinoma (RCC), optimizing the management of early stage RCC is critical
- For stage I and II RCC, surgery alone may be sufficient, with an expected 5-year DFS rate of 80%; patients with stage III or IV non-metastatic RCC with regional lymph node eventually relapse and progress to stage IV metastatic RCC[1]
- Based on risk stratification using the UISS,[2] up to 15% of patients with non-metastatic RCC who undergo nephrectomy are considered at high risk of recurrence and ~60% will relapse within 5 yr[3]
- S-TRAC was the only phase 3 trial of VEGF-targeted adjuvant treatment of renal cell carcinoma (RCC) to show clinical benefit; more recently, readouts of immuno-oncology directed trials also provided inconsistent results[4,5]
- Addition of genomics and/or transcriptomics biomarkers could potentially improve risk assessment and help identify patients at high risk of disease recurrence

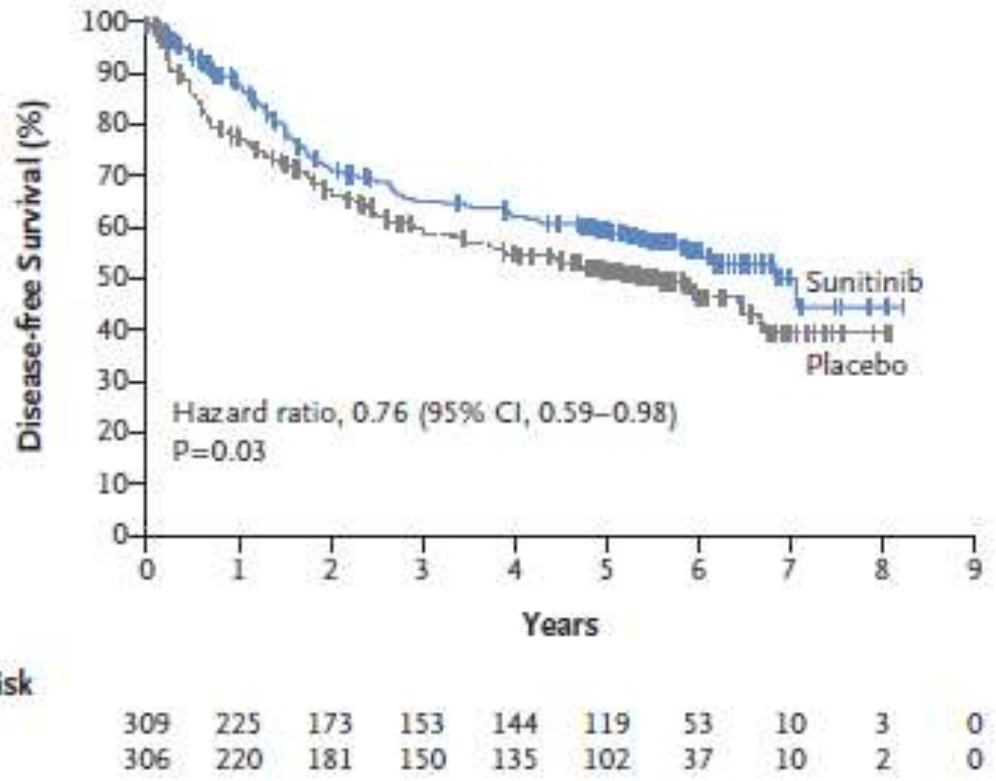
1. Tsui K-H, et al. J Urol 2000;163:1090-5. 2. Zisman A, et al. J Clin Oncol 2001;19:1649-57. 3. Lam JS, et al. J Urol 2005;174:466-72. 4. Choueiri TK, et al. N Engl J Med 2021; 385:683-694. 5. Pal SK, et al. Lancet 2022; 400: 1103–16.
DFS=disease-free survival; RCC=renal cell carcinoma; UISS=University of California Los Angeles Integrated Staging System

# The S-TRAC Trial: 2007-2017

- Sunitinib is a multi-targeted inhibitor of VEGF signaling pathway initially approved globally for treatment of metastatic RCC and, recently, by the FDA and other countries (but not the EMA) for adjuvant therapy in patients with high-risk recurrent RCC post nephrectomy[1]

- In the randomized phase III S-TRAC trial, adjuvant sunitinib (~1 year treatment) prolonged DFS over placebo in patients with locoregional RCC at high risk of recurrence following nephrectomy (HR 0.76, 95% CI 0.59–0.98; P=0.03)[2]

- At 5 years, the proportions of patients who were disease-free were 59.3% in the sunitinib group and 51.3% in the placebo group, for an absolute risk reduction of 8%[2]




1. Sutent (sunitinib malate) prescribing information. Pfizer Inc, 2022. 2. Ravaud A, et al. N Engl J Med 2016;375:2246-54.
CI=confidence interval; DFS=disease-free survival; HR=hazard ratio; VEGF=vascular endothelial growth factor

# Objectives

- To conduct an exploratory, hypothesis-generating analysis of tumor tissue obtained prospectively from a large, global phase III trial of patients rendered disease-free by nephrectomy, who are at high risk of RCC recurrence and treated with adjuvant anti-angiogenic therapy (sunitinib) or placebo, to identify new prognostic/predictive biomarkers including gene expression signatures (GES) associated with poor outcome and short DFS

# Methods (I)

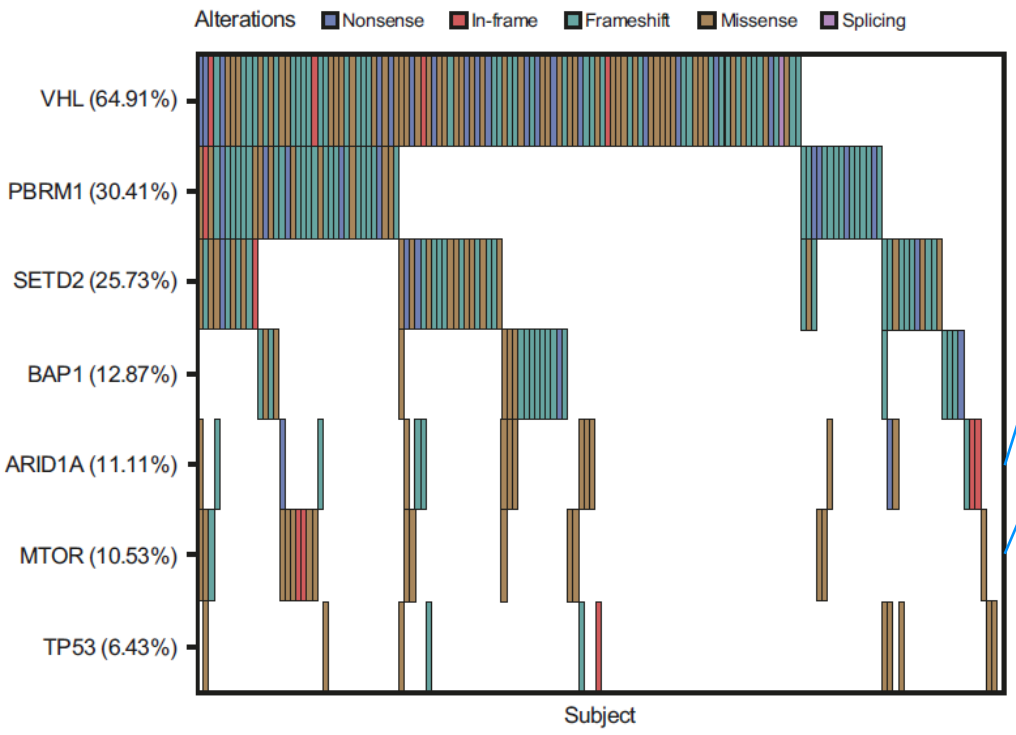
- Study design
  - 615 patients were randomly assigned (1:1) to receive sunitinib (50 mg/day) or placebo on a 4-days-on/2-days-off schedule for 1 year or until disease recurrence, diagnosis of secondary malignancy, unacceptable side effect, or consent withdrawal
- Key eligibility criteria
  - Clear-cell, locoregional (≥T3 and/or N+) RCC
  - ECOG PS 0–2 before nephrectomy
  - No prior systemic therapy
  - Lack of macroscopic residual or metastatic disease, by blinded ICR
- Whole exome and transcriptome sequencing
  - Archival de-identified FFPE tumor tissue blocks from nephrectomy or tumor biopsy were obtained from patients who provided informed consent for genomic analyses.
  - Using the Accuracy and Content Enhanced [ACE] version 3 platform ( on Illumina NovaSeq), resulting sequences were processed by the Personalis ACE Cancer Exome pipeline (Personalis, Inc, Menlo Park, CA).

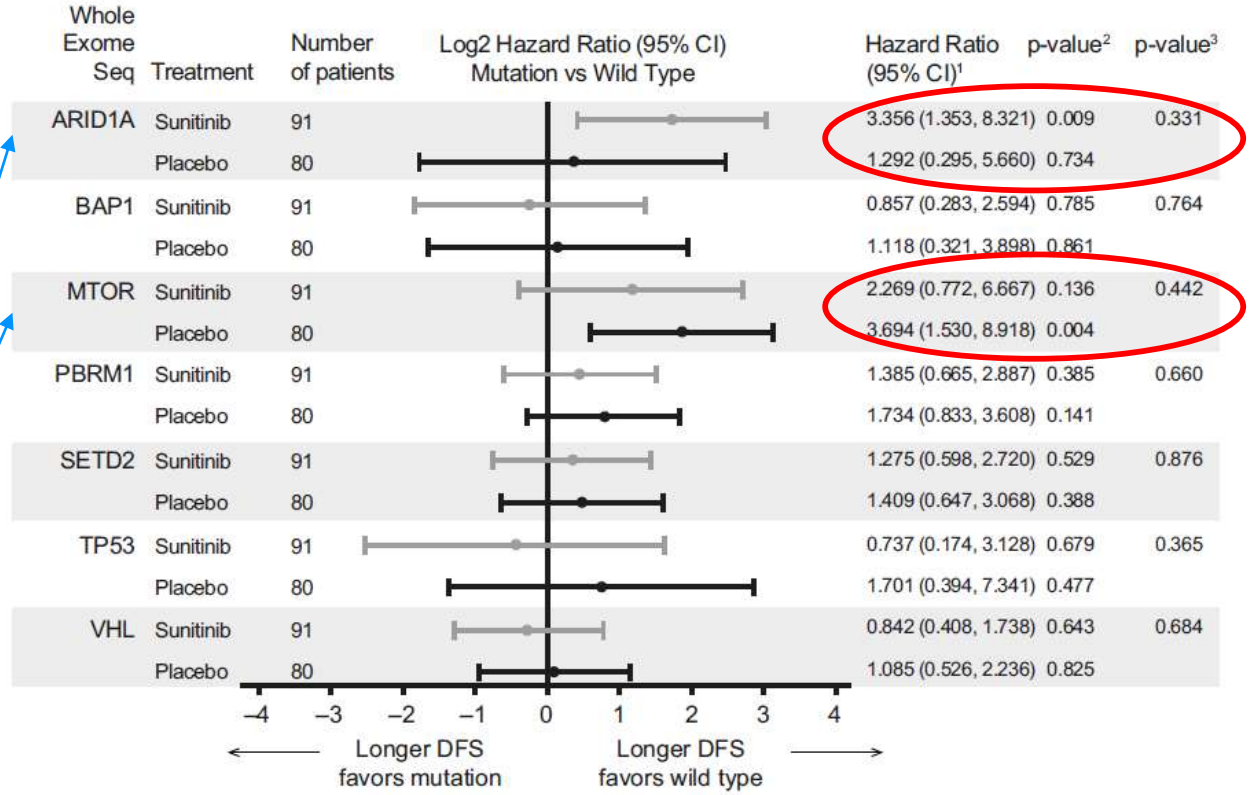
# Methods (II)

- Gene expression signature analyses
  - GES analyses included published signatures from the IMmotion 150 study [Teff, angiogenesis, myeloid inflammation (Minf)], and the JAVELIN Renal 101 study [Immune, angiogenesis][1,2]
- Elastic net analysis.
  - Multi-feature signatures were derived using samples with complete data from the sunitinib arm for STRAC11, the placebo arm for STRAC14, and from both arms for STRAC13.
  - These GES were further verified using two independent datasets, the JAVELIN Renal 101 study in patients with metastatic advanced RCC (n= 720) and the KIRC dataset of TCGA (n = 488).
- Quantification and statistical analysis
  - For gene expression analyses, DFS by BICR was compared between biomarker stratum by <median vs ≥median values of a particular parameter using Kaplan–Meier analysis. DFS was also compared between the two treatment groups within a biomarker stratum using the Kaplan–Meier method. For the mutational analyses, Cox proportional hazards model with wild-type samples as the reference group was used to calculate HR and 95% CI.
  - No adjustments of *p*-values or CIs for multiplicity were performed.

1. McDermott, D F et al.. Nat. Med. 2018; 749–757. 2. Motzer, R J et al. Nat. Med. 2020; 1733–1741.

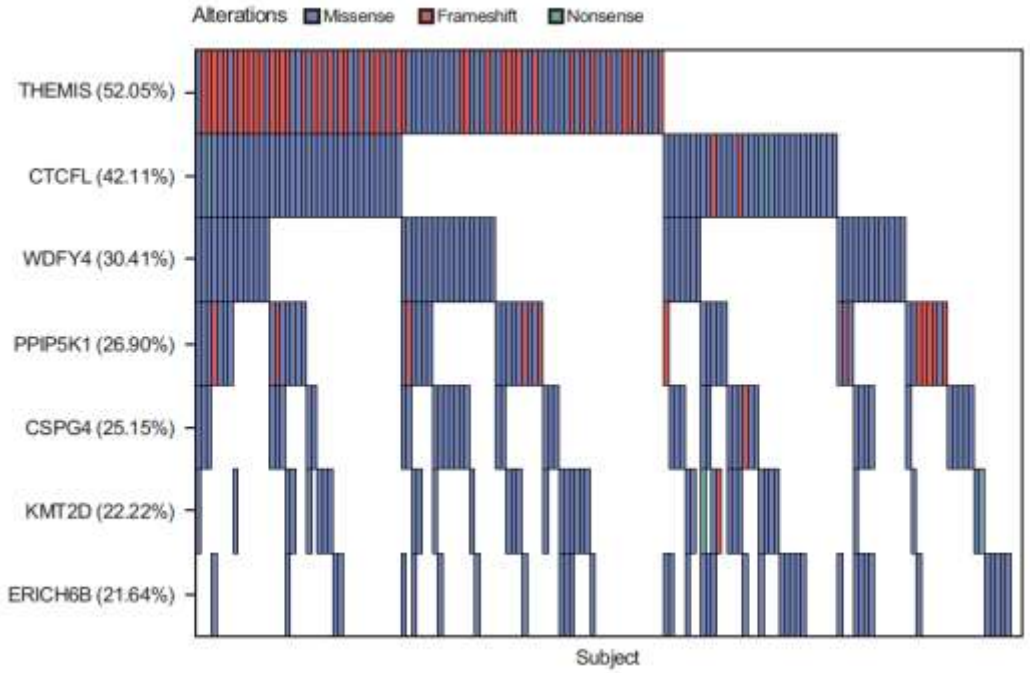
# Classic ccRCC mutations do not predict outcome following tumor resection

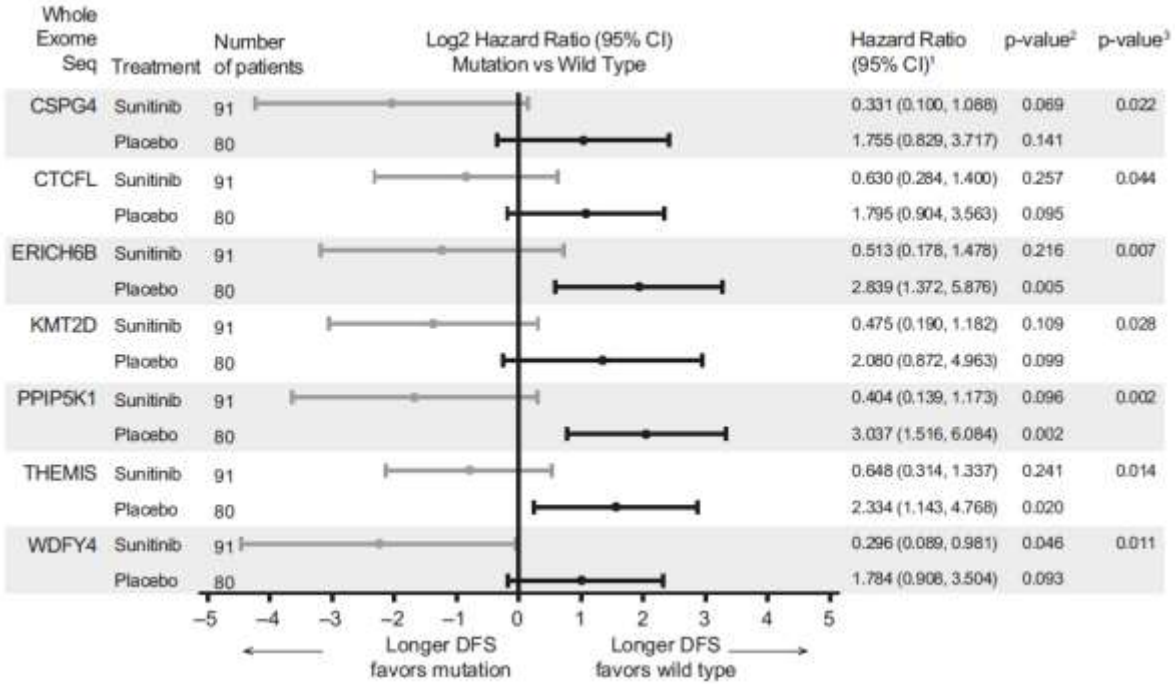



- Treatment arm–specific differences in DFS relative to wild-type when mutations in *ARID1A*
- *MTOR* mutations are associated with poor prognosis
  - In our cohort of patients enriched with clinical characteristics of high risk of recurrence, the frequency of *MTOR* mutations was slightly higher, at 10.5% (versus ~6%)

# Mutations in immune-related or chromatin homeostasis genes influenced treatment outcome

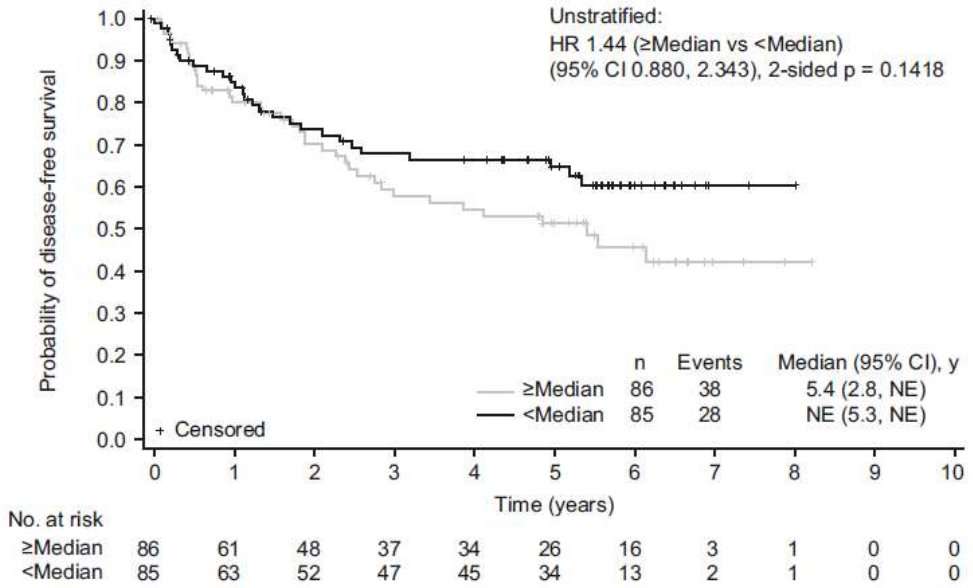


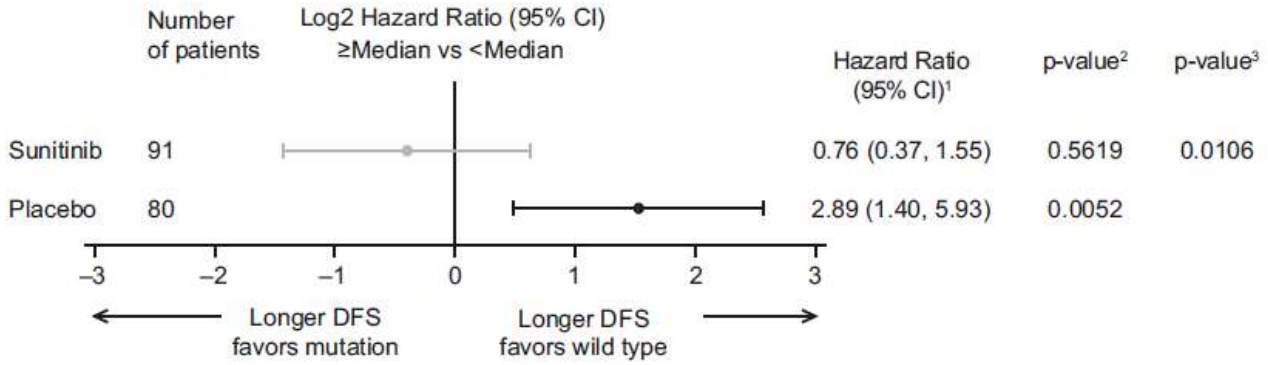




- Variants in either *THEMIS*, *WDFY4*, or *CSPG4* (involved in T-cell activity and maintenance) that did not predict outcome in the overall population but were associated with longer DFS in sunitinib-treated patients.
- Mutations in *CTCFL*, *KMT2D*, *PPIP5K1*, and *ERICH6B* were also associated with longer DFS in sunitinib-treated patients

1. Cox proportional hazards model with <median as the reference group was used to calculate HR and 95% CI. 2. Cox regression HR p-value is used to compare between Wild Type/Mutation groups. A HR <1 indicates better survival in the Mutation group, while a HR >1 indicates better survival in the Wild Type group. HR reference level is <median, p-value is from Logrank test. 3. Two-sided p-value for overall Wild Type/Mutation-by-treatment interaction from Cox model with treatment group and wild-type/mutation status as two independent variables..

# High tumor mutational burden (TMB) is associated with poor prognosis

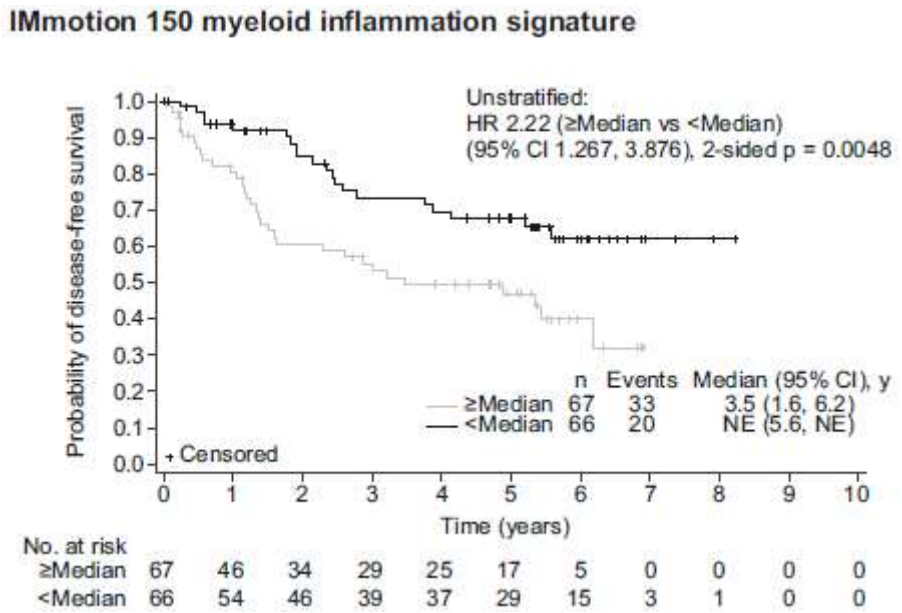


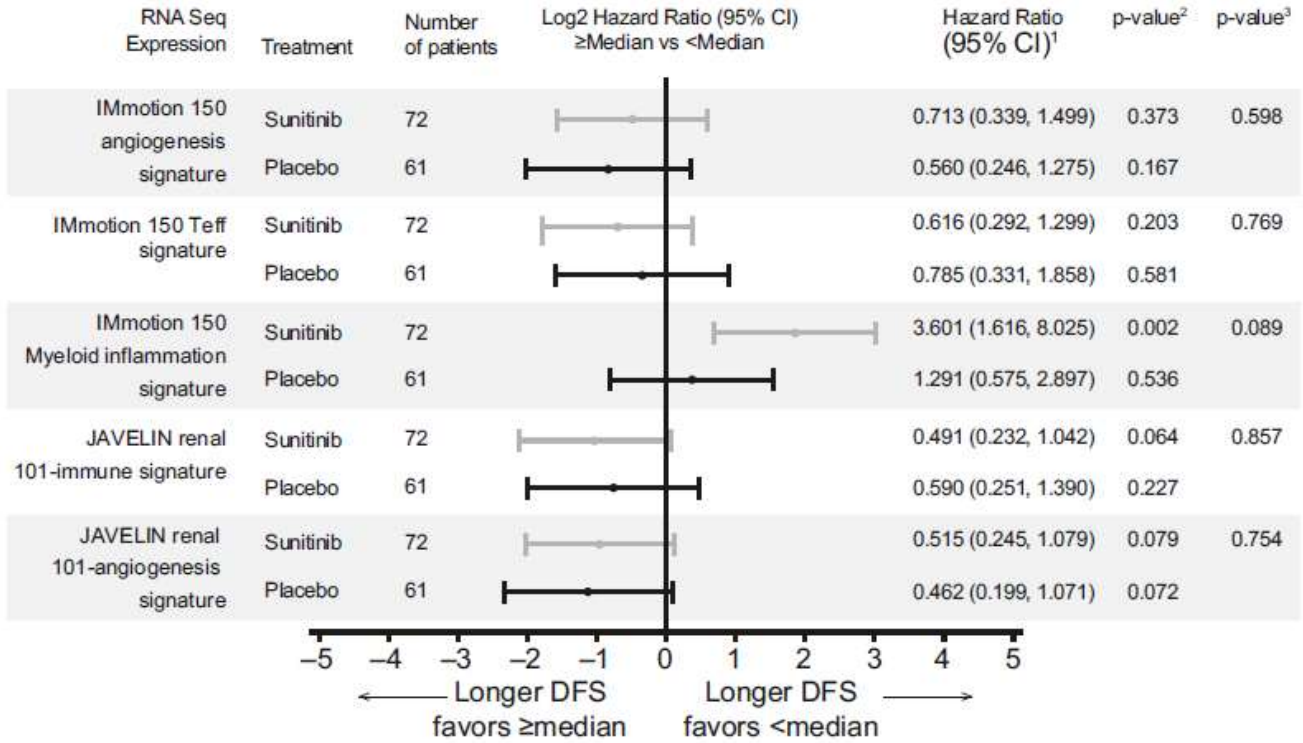




- High TMB effect may be confounded with a clinical benefit to adjuvant sunitinib

Low versus high TMB (based on median cutoff, without using a pre-set cutoff of 10 or 20 mutations per Mb)

# Previously defined immune and angiogenic-associated transcriptomic signatures predict outcome in the overall cohort population

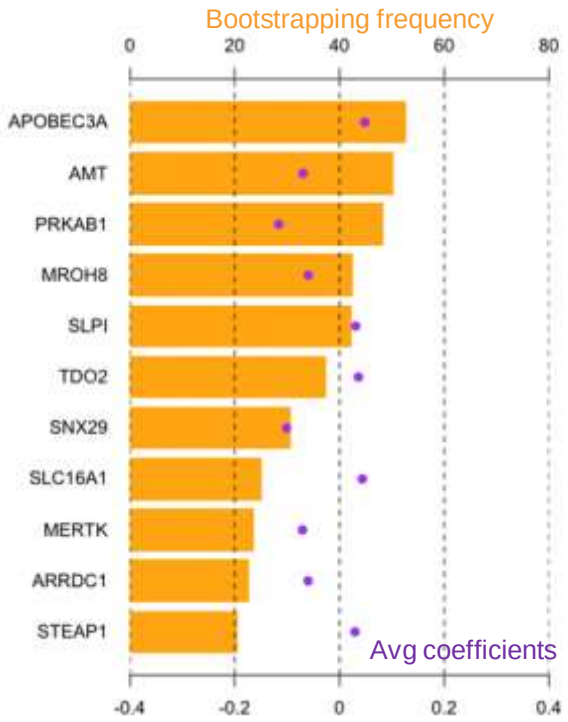


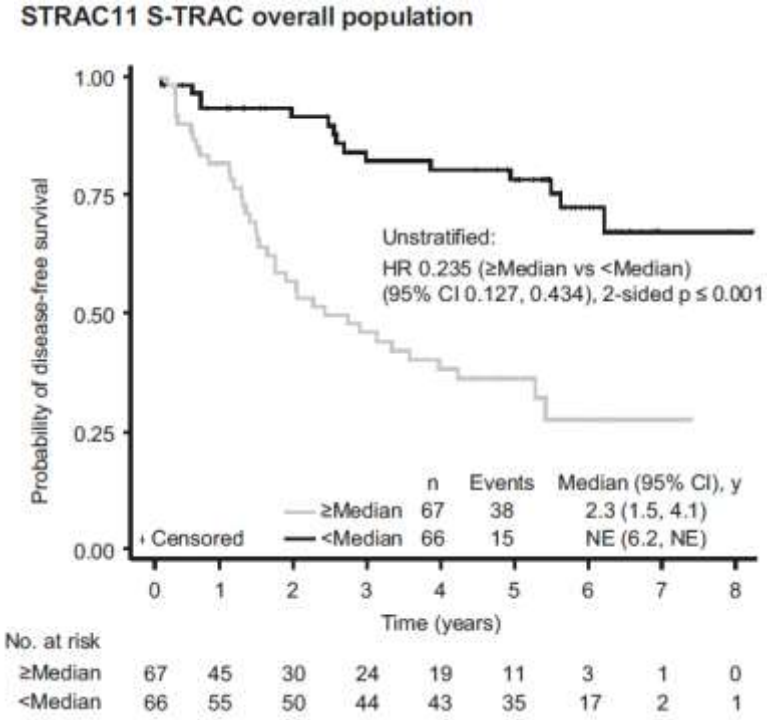



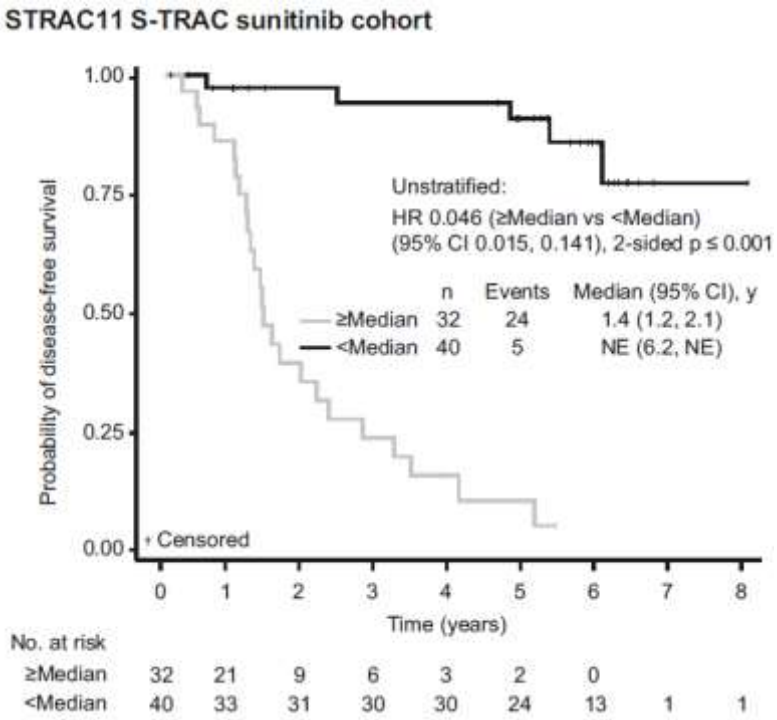

- Both IMmotion 150[4] and JAVELIN Renal 101[5] utilized sunitinib (standard of care at the time for advanced/metastatic stage disease) as comparator arm.
- In sunitinib-treated group, longer DFS was associated with lower expression of the myeloid inflammation GES (HR 3.60 [95% CI: 1.62–8.03])

1. Cox proportional hazards model with <median as the reference group was used to calculate HR and 95% CI. 2. Cox regression HR p-value is used to compare between overall median cutoff groups. A HR <1 indicates better survival in the ≧Median group, while a HR >1 indicates better survival in the <Median group. HR reference level is <median, p-value is from Logrank test. 3. Two-sided p-value for overall median cutoff-by-treatment interaction from Cox model with treatment group and median cutoff status as two independent variables. HR analyses are adjusted for sex and age (<65, ≥65), using proportional hazards modeling. No adjustments were made for multiple comparisons. 4. McDermott, D F et al.. Nat. Med. 2018; 749–757. 5. Motzer, R J et al. Nat. Med. 2020; 1733–1741

# Elastic net combinatorial biomarker approach identified transcriptomic signatures associated with high risk of recurrence and poor prognosis



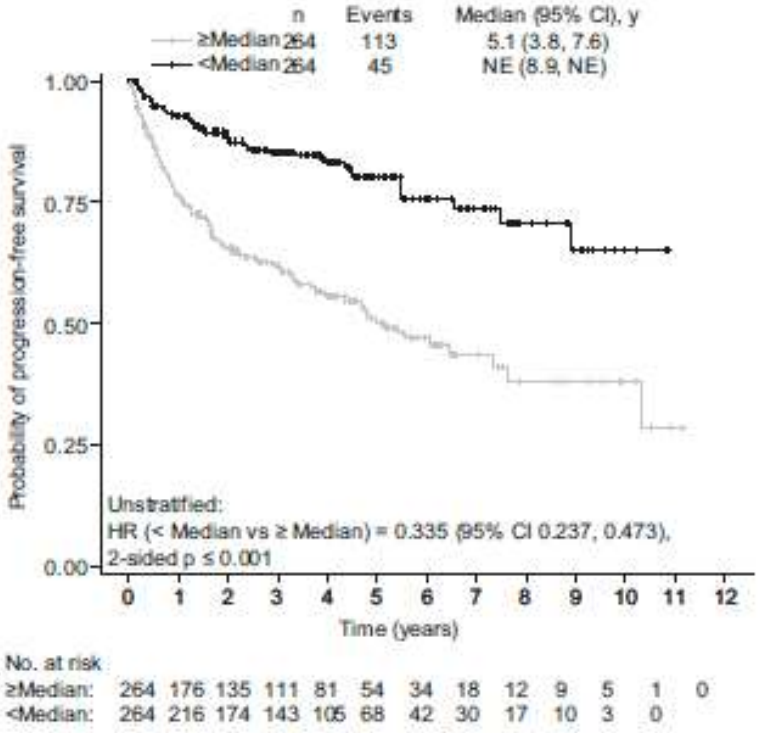

- Using the sunitinib treatment arm dataset only, we identified a GES that consists of 11 genes (STRAC11) associated with greater benefit in a subgroup of patients.

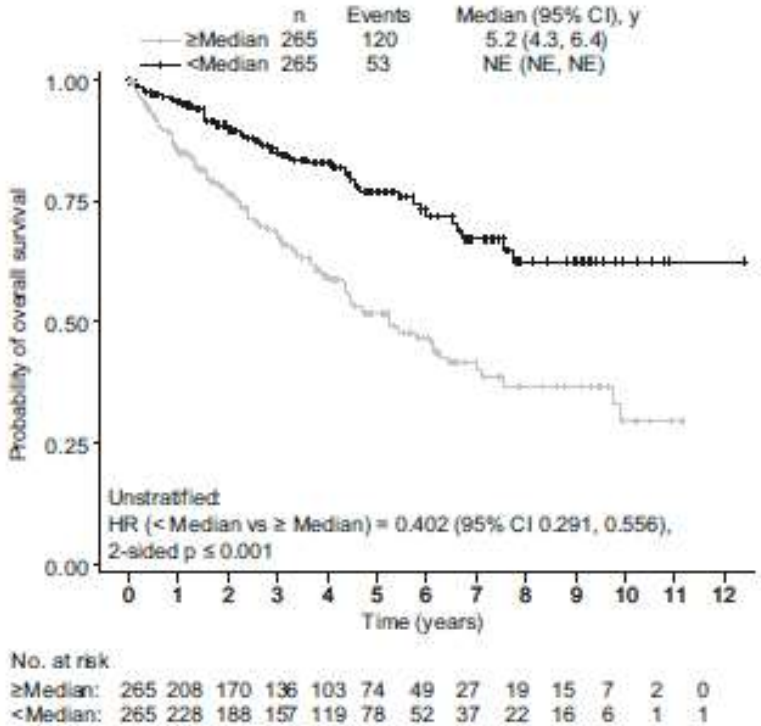
# STRAC11 signature

| | | |
|---|---|---|
| STRAC11 | *APOBEC3A* | Apolipoprotein B MRNA Editing Enzyme Catalytic Subunit 3A; induces mutagenesis in cancer cells, and contributes to tumor evolution |
| | *PRKAB1* | Protein Kinase AMP-Activated Non-Catalytic Subunit Beta 1; a regulatory subunit of the AMP-activated protein kinase (AMPK), can act as either a tumor suppressor (prevent tumorigenesis) or a tumor promoter (after tumorigenesis occurred) |
| | *MROH8* | Maestro Heat Like Repeat Family Member 8 |
| | *SLPI* | Secretory Leukocyte Peptidase Inhibitor; modulates the inflammatory and immune responses and the promotion of cell proliferation |
| → | *TDO2* | Tryptophan 2,3-Dioxygenase; may play a role in cancer through the suppression of antitumor immune responses |
| | *SNX29* | Sorting Nexin 29; circular RNA derived from this gene reduced myoblast proliferation and promoted cell differentiation |
| | *SLC16A1* | Solute Carrier Family 16 Member 1; a key controller of the cell cycle and mitosis, oncogene role in promoting cancer cell proliferation |
| → | *MERTK* | MER Proto-Oncogene, Tyrosine Kinase; regulates cell survival, migration, differentiation, and phagocytosis of apoptotic cells; increases tumor immunogenicity |
| | *ARRDC1* | Arrestin Domain-Containing 1; a tumor suppressor in ccRCC in the Hippo pathway |
| | *STEAP1* | Six Transmembrane Epithelial Antigen Of The Prostate 1; promotes proliferation, migration, invasiveness, and tumorigenicity |

- Following coexpression and network analyses, this signature was found to be enriched for genes involved in the regulation of the stroma component of the tumor (TDO2, STEAP1) as well as Treg cells (SLC16A1, PRKAB1) and myeloid cell (APOBEC3A, MERTK, SNX29) subsets

# STRAC11 GES verification in the advanced RCC setting: TCGA KIRC dataset

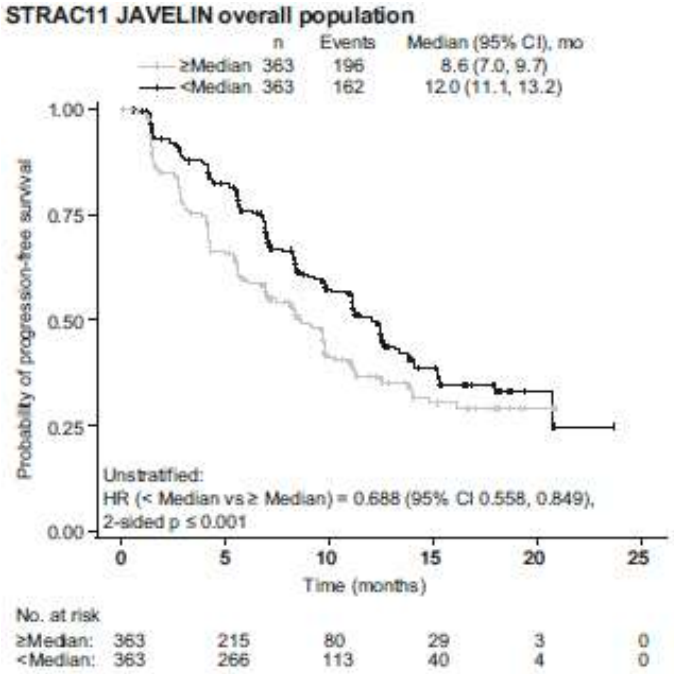


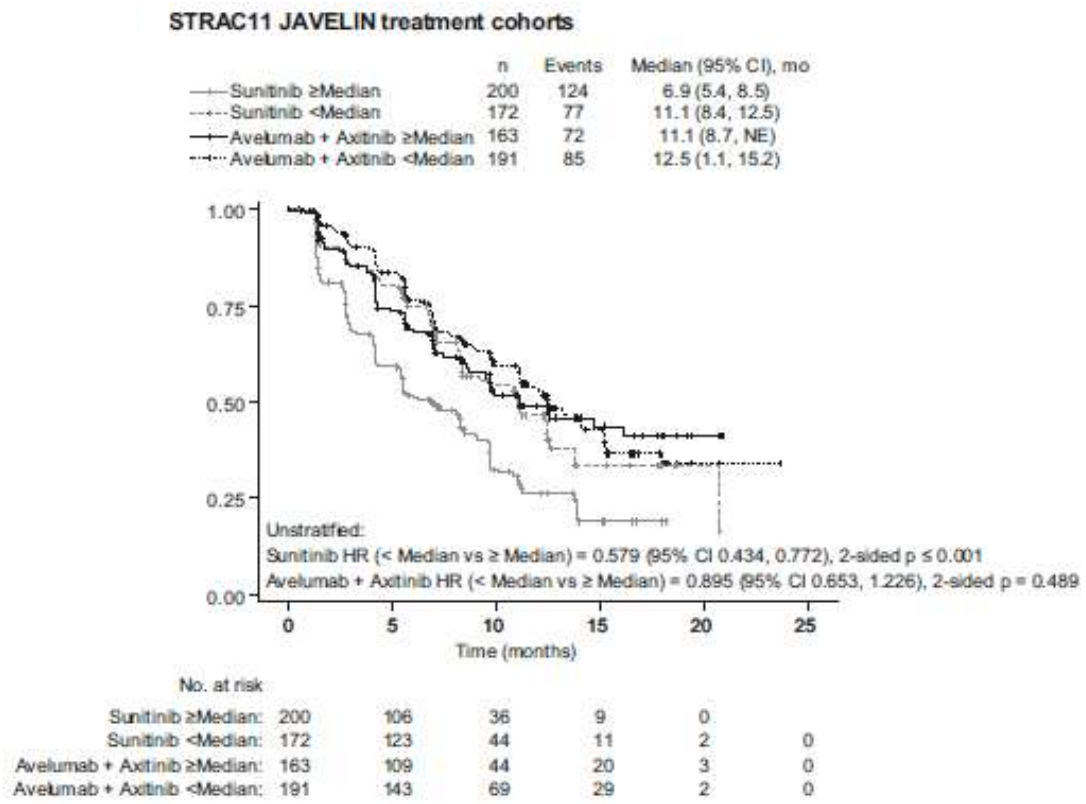




- Low versus high expression of STRAC11 GES was associated with longer PFS and OS

(Cancer Genome Atlas Research, 2013). Patient cases that have received VEGFR TKI, have the gene expression data set and have PFS and/or OS data available.

# STRAC11 GES verification in the advanced RCC setting: JAVELIN Renal 101 metastatic RCC population




- Low versus high expression of STRAC11 GES was associated with longer PFS in the sunitinib treatment arm, not in the avelumab+axitinib arm

Motzer, R J et al. Nat. Med. 2020; 1733–1741.

# Conclusions

- Mutations in specific genes were associated with worse outcomes in the placebo arm, but not so often in the sunitinib arm.
- *MTOR* mutations are a poor prognosis marker, and MTORC1 is a relevant target for this patient population (EVEREST trial[1])
- The immunosuppressive environment of the micrometastasis at the nesting site is likely as important as the angiogenic phenotype in identifying effective therapy in the adjuvant RCC setting.
- In addition to antiangiogenic agent, adjuvant therapy should aim at targeting some of the key elements captured in the GES discovered in this study, e.g, MER (myeloid cells), TDO2 (stroma), etc.

These findings may inform therapeutic strategies and more personalized approaches for adjuvant therapy in patients with RCC at high risk of recurrence.

1. Rryan CW et al. Clin Oncol 40, no. 17_suppl (June 10, 2022) LBA4500

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## Molecular characterization of renal cell carcinoma tumors from a phase III anti-angiogenic adjuvant therapy trial

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