

# Single nucleotide polymorphisms as predictors of response and toxicity in advanced clear cell renal cell carcinoma patients treated with first line sunitinib



**Cristina Rodríguez-Antona**

Hereditary Endocrine Cancer Group  
Human Cancer Genetics Programme  
Spanish National Cancer Center (CNIO)

E-mail: [crodriguez@cniio.es](mailto:crodriguez@cniio.es)

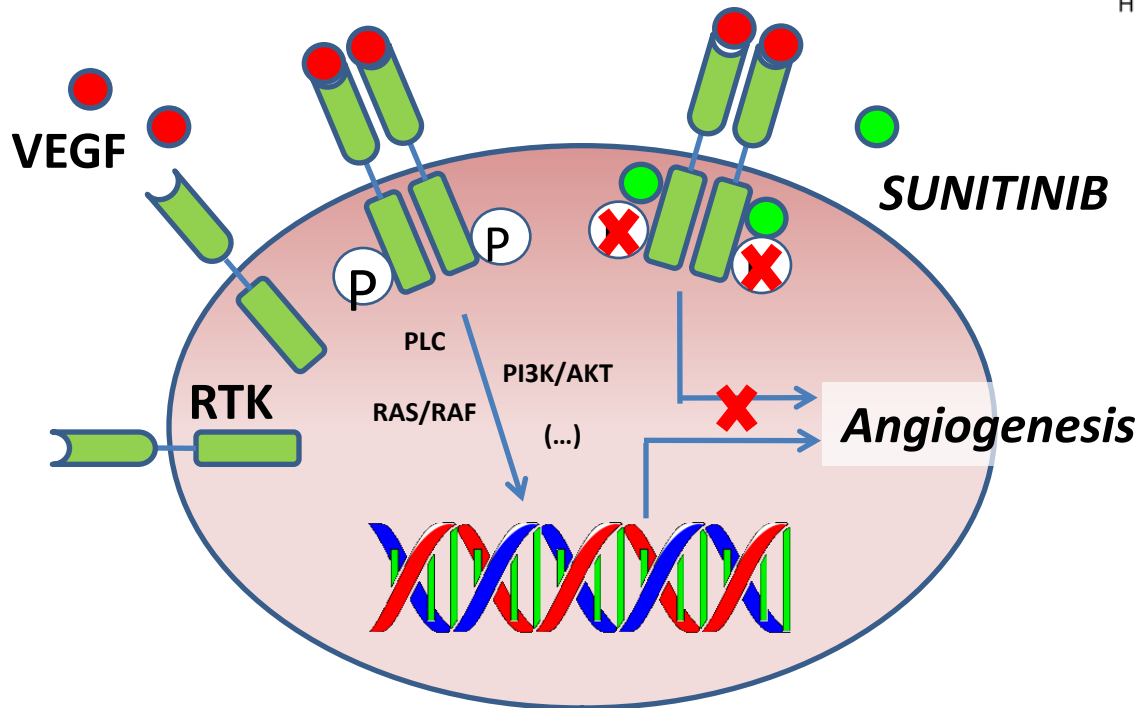
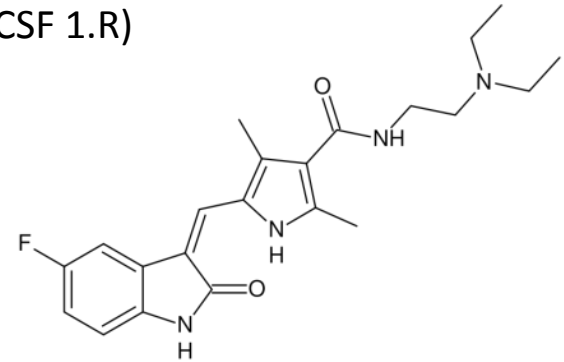
**V CONGRESO SEFF**

*"El Laboratorio dialoga con la Clínica"*



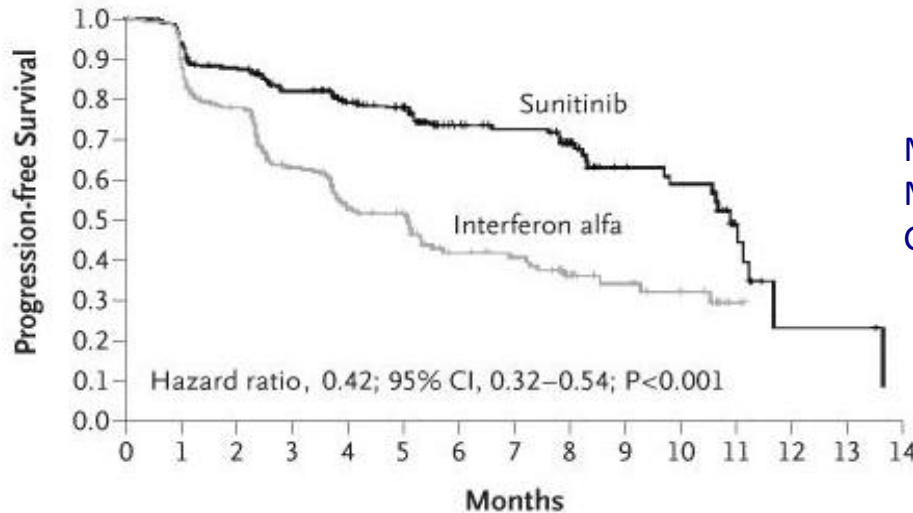
# Sunitinib

- Oral multi-targeted receptor tyrosine kinase inhibitor  
(VEGFR1, VEGFR2, VEGFR3, PDGFR- $\alpha$ , PDGFR- $\beta$ , KIT, FLT-3, RET, CSF 1.R)
- Anti-angiogenic and antitumor effects



# Sunitinib treatment for renal cancer

- Standard first line treatment for advanced renal cell carcinomas (RCC)



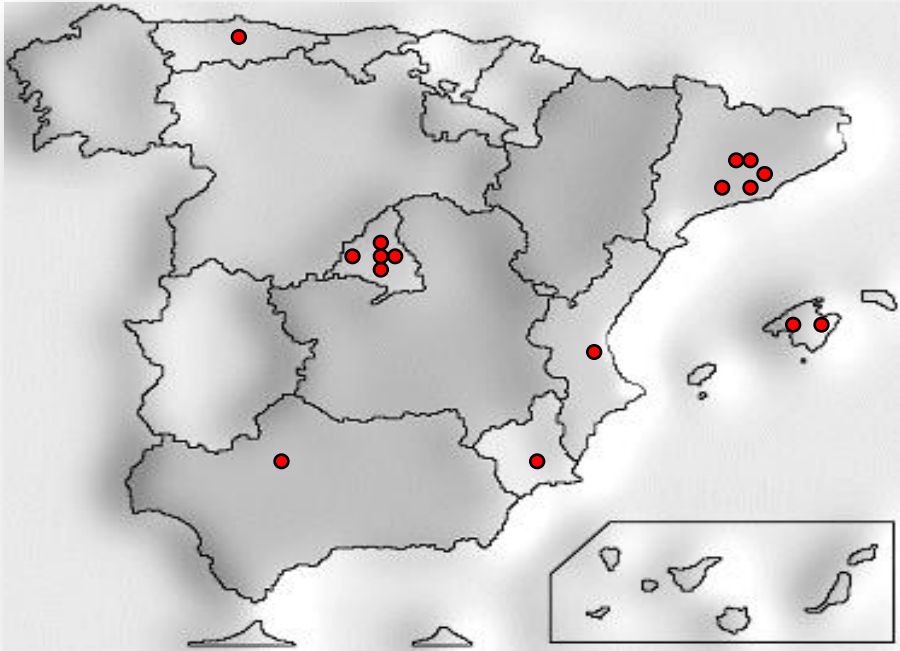
Motzer *et al.* *N Engl J Med* 2007; **356**:115  
Motzer *et al.* *J Clin Oncol* 2009; **27**:3584  
Gore *et al.* *Lancet Oncol* 2009; **10**:757

- Clinical problems:
  - 20% develop early progression of the disease
  - Dose suspensions (8%) and reductions (32%) due to toxicity

Find biomarkers predictive of sunitinib resistance and toxicity

# Multicenter prospective study

Samples obtained from 15 Spanish Hospitals (SOGUG)



## Design

- Sunitinib in daily practice setting

## Recruitment

- Oct 10, 2007 – Dec 13, 2010

## Inclusion criteria

- 18 y-old or older
- Clear cell
- Metastatic/ non resectable
- Life expectancy >3 months
- Evaluable disease
- Written consent

## Exclusion criteria

- Any prior treatment (cytokines)

# Patient and clinical characteristics

Characteristic	Nr.	%
<b>Age at sunitinib (y)</b>	65	
Range	56-73	
<b>Sex</b>		
Male	65	68
Female	30	32
<b>ECOG</b>		
0	25	26
1	56	59
2	8	8
3	0	0
Missing	6	6
<b>Previous nephrectomy</b>		
Yes	76	80
No	19	20
<b>Nr. metastatic sites</b>		
0	2	2
1	27	28
2	44	46
>3	22	23
<b>MSKCC risk factors<sup>a</sup></b>		
0 (favorable)	42	44
1-2 (intermediate)	50	53
≥3 (poor)	3	3
<b>Initial sunitinib dose</b>		
50 mg	84	88
37.5 mg	9	9
25 mg	2	2

- 95 patients for toxicity, 89 for efficacy

- Follow up: 21.2 m (95% CI=13.6-28.9)
- Progression free survival: 12.3 m
- 62 (70%) alive at analysis
- Objective response in 78 patients with measurable disease:
  - 1 CR (1%)
  - 36 PR (46%)
  - 6 SD (33%)
  - 15 PD (19%)

- Most common toxicities: asthenia, mucositis, diarrhea, neutropenia, and HFS
- Grade 3 adverse events: 43 (45%)
- Dose reductions due to toxicity 47 (49%)

# Methods

- **Samples**

Peripheral blood/saliva for DNA extraction

- **Polymorphisms selection: 16 SNPs**

- Pharmacodynamics
- Pharmacokinetics

- **Genetic model**

- Additive

- **Statistical analysis**

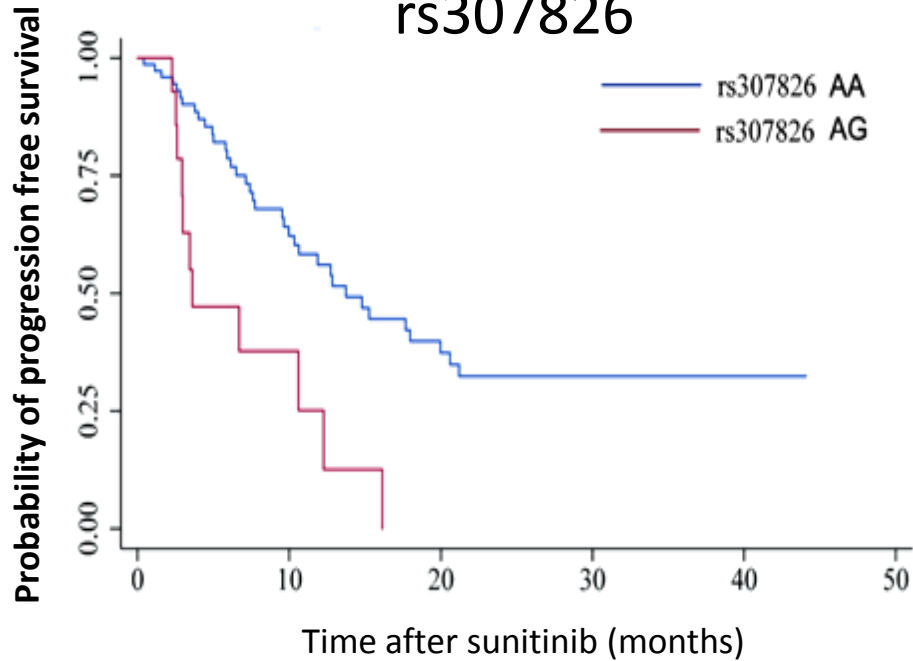
- Multivariable including relevant clinical factors
- Bonferroni correction for multiple testing

Gene	SNP	Variation	MAF <sup>a</sup>
<i>VEGFR2</i>	rs2305948 C>T	V297I	0.100
<i>VEGFR2</i>	rs1870377 T>A	Q472H	0.263
<i>VEGFR3</i>	rs307826 A>G	T494A	0.079
<i>VEGFR3</i>	rs448012 C>G	H890Q	0.404
<i>VEGFR3</i>	rs307821 G>T	R1324L	0.095
<i>PDGFR-α</i>	rs35597368 T>C	S478P	0.105
<i>VEGF-A</i>	rs2010963 G>C	5'UTR	0.311
<i>VEGF-A</i>	rs699947 A>C	Promoter	0.468
<i>VEGF-A</i>	rs1570360 G>A	Promoter	0.311
<i>IL8</i>	rs1126647 A>T	3'UTR	0.372
<i>CYP3A4</i>	rs2740574 A>G	Promoter	0.027
<i>CYP3A5</i>	rs776746 G>A	Splicing	0.064
<i>ABCB1</i>	rs1045642 C>T	I1145I	0.441
<i>ABCB1</i>	rs1128503 C>T	G412G	0.384
<i>ABCB1</i>	rs2032582 G>T	A893S	0.375
<i>ABCG2</i>	rs2231142 C>A	Q141K	0.053

# Progression free survival

## VEGFR3

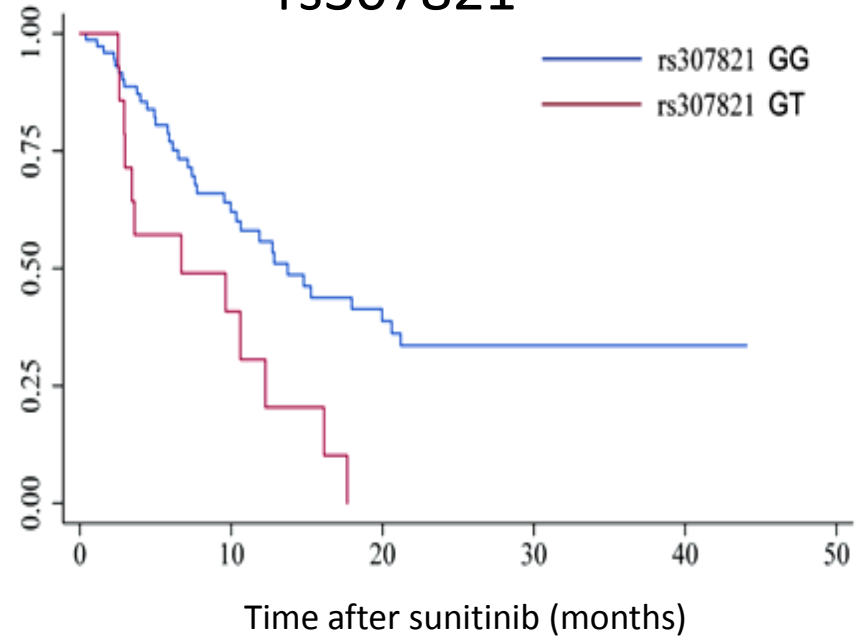
rs307826



**HR = 3.6 (1.7-7.3)**

**$P_{\text{unadjusted}} = 0.0005$ ,  $P_{\text{adjusted}} = 0.008$**

rs307821



**HR = 3.3 (1.6-6.7)**

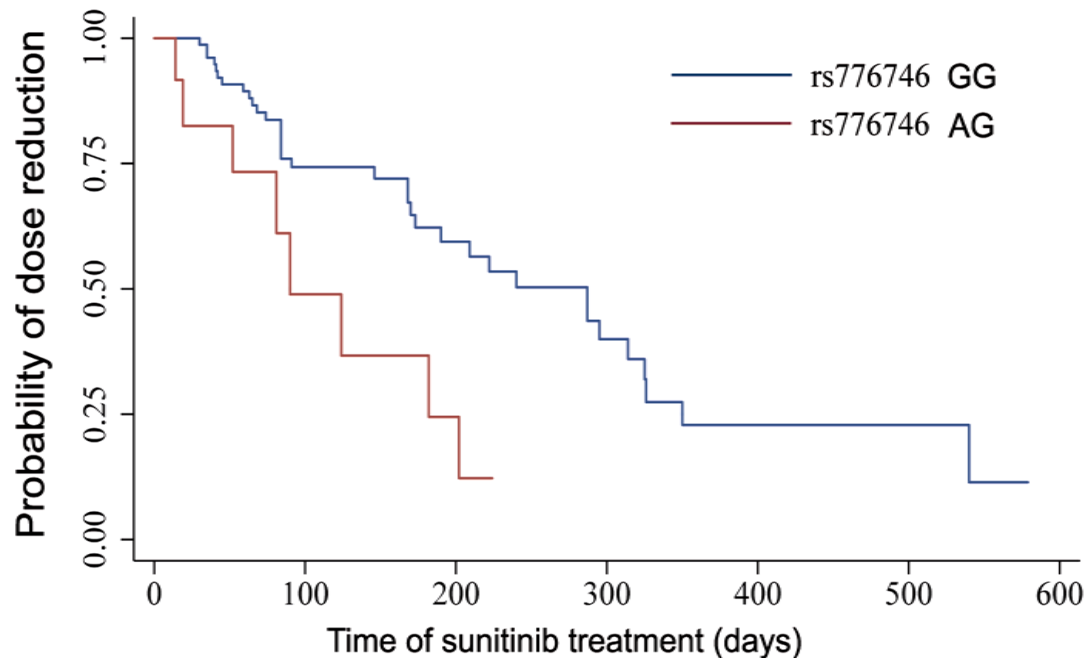
**$P_{\text{unadjusted}} = 0.0008$ ,  $P_{\text{adjusted}} = 0.014$**

\*Multivariable analysis (gender, MSKCC risk factors)

Lancet Oncology (in press)

# Dose reductions due to toxicity

## *CYP3A5*



**HR = 3.7 (1.7-8.4),  $P_{\text{unadjusted}} = 0.0014$ ,  $P_{\text{adjusted}} = 0.022$**

\*Multivariable analysis (gender  $P=0.005$ )

Lancet Oncology (in press)

# Conclusions

- Two *VEGFR3* polymorphisms (rs307826 and rs307821) define a subset of RCC patients with a decreased sunitinib efficacy
- Patients carrying *CYP3A5\*1* allele exhibited a higher risk of sunitinib dose reductions due to toxicity
- These markers could lead to therapeutic approaches for these two specific populations (alternative antiangiogenic drugs and mTOR inhibitors)

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