Manejo de los efectos adversos.

¿Factores predictivos de respuesta?

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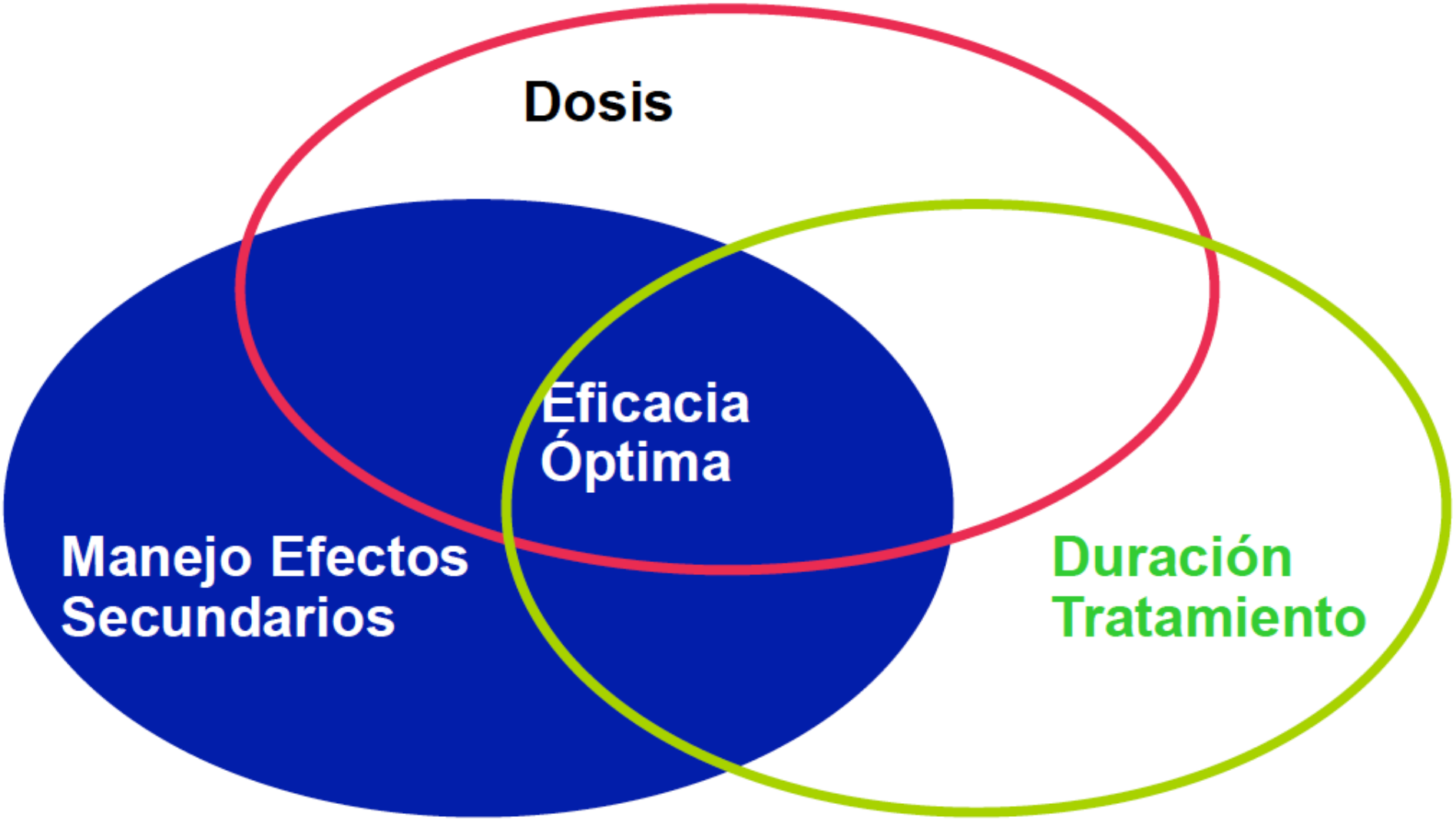
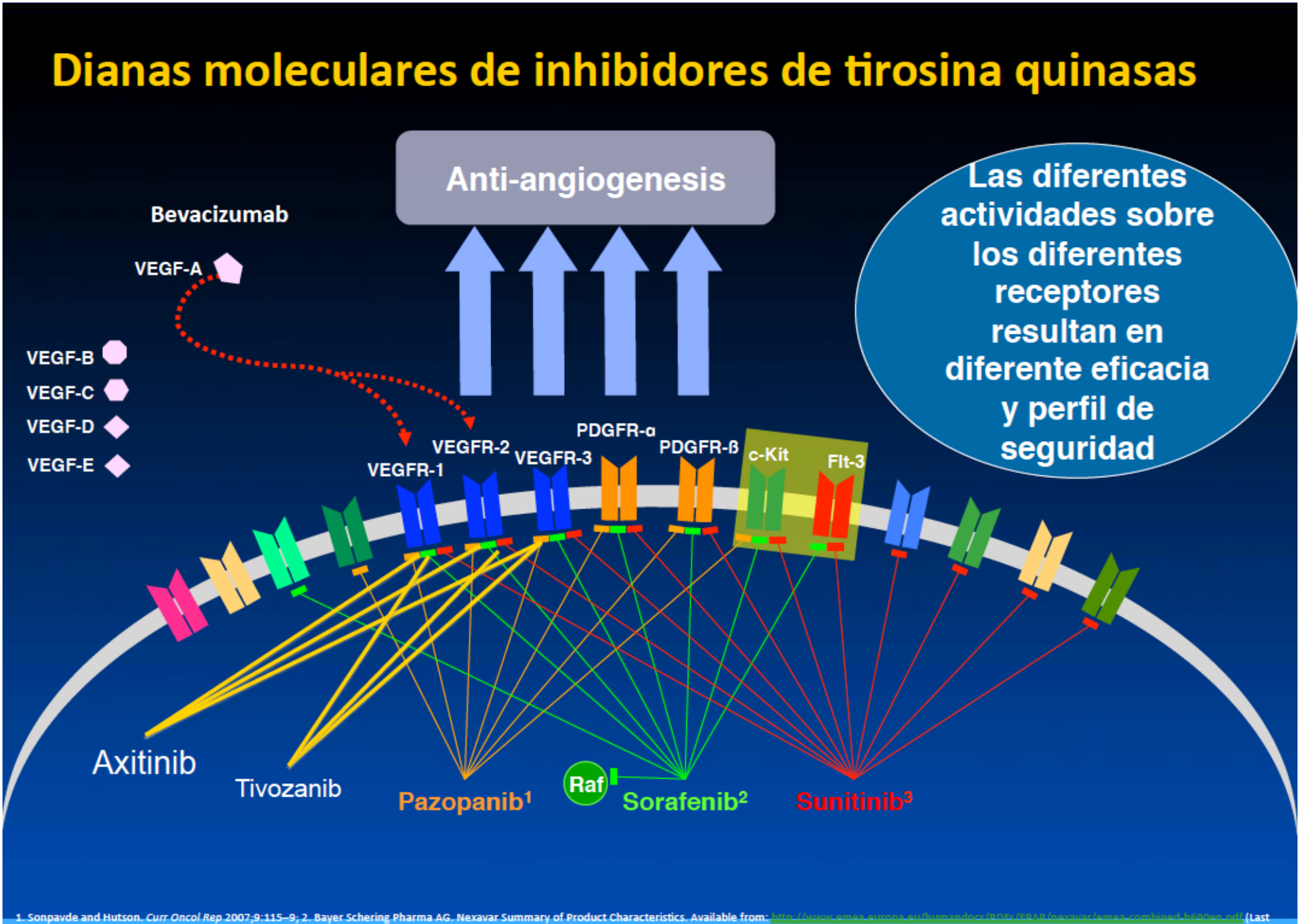
Tres factores claves para el éxito de la terapia en CCRm

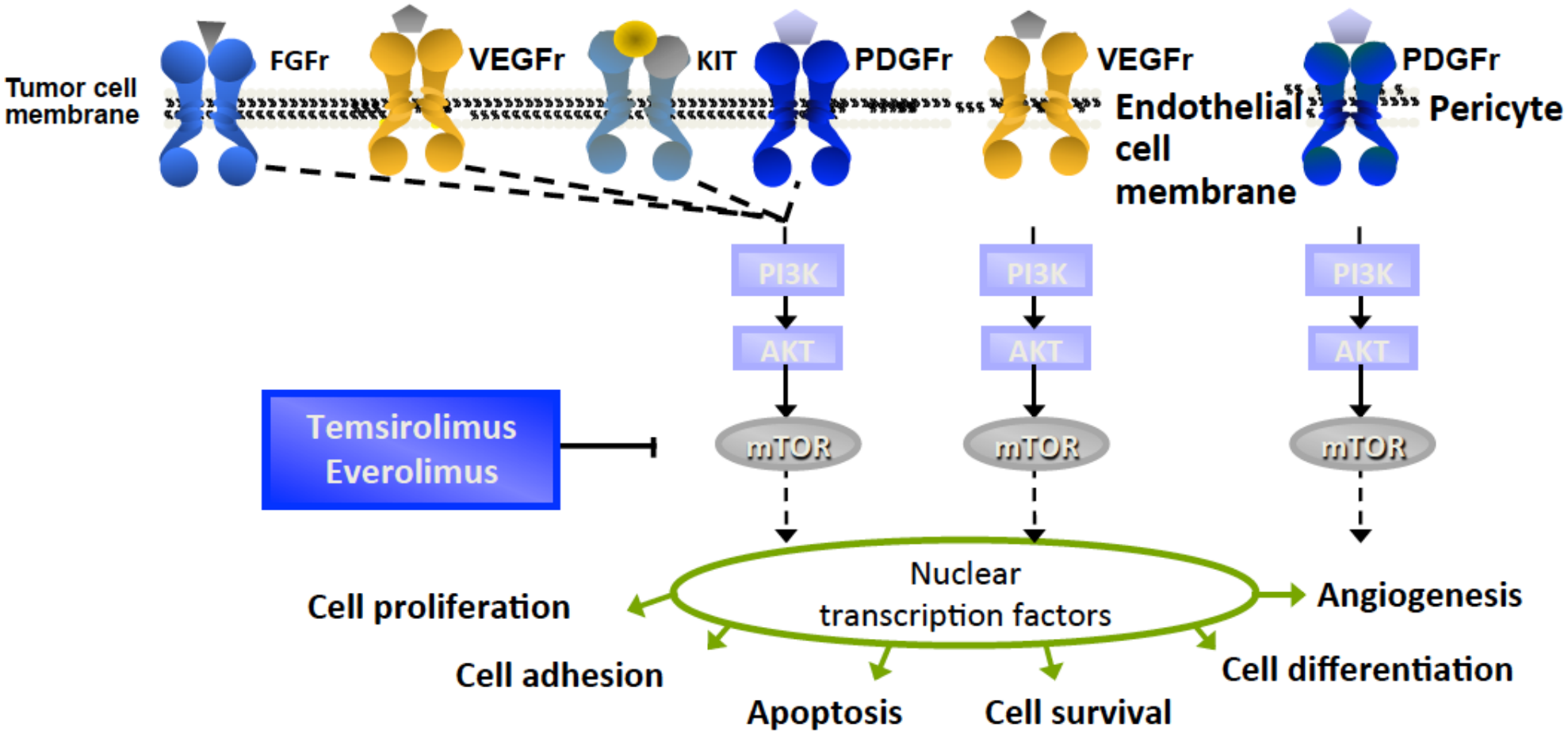


Dianas moleculares de inhibidores de tirosina quinasas



1. Sonpavde and Hutson. *Curr Oncol Rep* 2007;9:115–9; 2. Bayer Schering Pharma AG. Nexavar Summary of Product Characteristics. Available from: http://www.emea.europa.eu/humandocs/PDFs/EPAR/nexavar/emea-combined-h688en.pdf (Last accessed February 2010); 3. Pfizer Italia S.r.l. Sutent Summary of Product Characteristics. Available from: http://www.emea.europa.eu/humandocs/PDFs/EPAR/sutent/emea-combined-h687en.pdf (Last accessed February 2010).

Mecanismos potenciales para actuar los agentes diana inhibidores kinasa (IK)[1-3]



1. Rini BI, Small EJ. *J Clin Oncol.* 2005;23:1028-1043. 2. Rini BI. *J Clin Oncol.* 2009;27:3225-3234.
3. Korc M, Friesel RE. *Curr Cancer Drug Targets.* 2009;9:639-651.

Eventos Adversos relacionados con agentes diana

Adverse Event	Bevacizumab	Sunitinib	Sorafenib	*Pazopanib	Temsirolimus	Everolimus
Fatigue	++	++	++	+	+	++
Rash	–	+	++	–	++	++
Hand–foot syndrome	–	+	++	–	–	–
Hypertension	+	+	+	+	–	
Diarrhea	+	++	++	++	+	+
Stomatitis	–	++	+	–	++	++
Myelosuppression	–	++	–	+	+	+
Metabolic syndrome	–	+	–	+	++	++
Epistaxis/bleeding	+	–	–		–	
Proteinuria	++	+	+	+	–	–
Liver toxicity	-	+	+	++	-	-
Discontinuation AE		20%		24%		

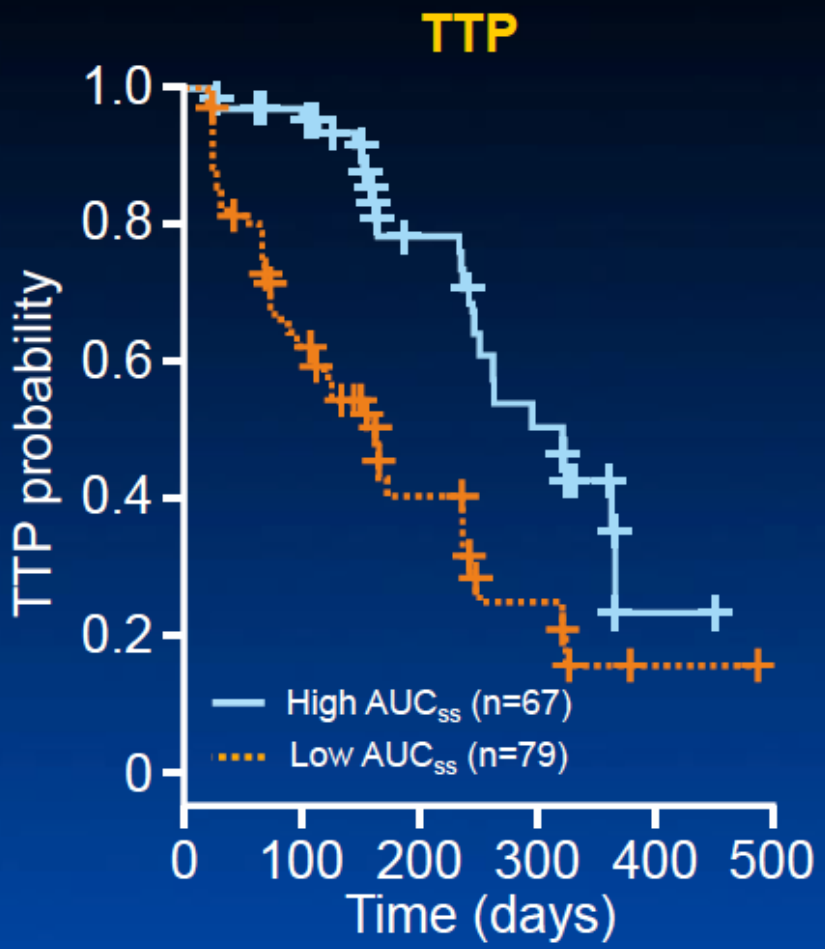
Escudier B, et al. *J Clin Oncol* 2010; Rini B, et al. *J Clin Oncol* 2010; Motzer RJ, et al. *J Clin Oncol* 2009; Escudier B, et al. *N Engl J Med* 2007; Sternberg C, et al. *J Clin Oncol* 2010; Hudes G, et al. *N Engl J Med* 2007; Motzer RJ, et al. *Cancer*

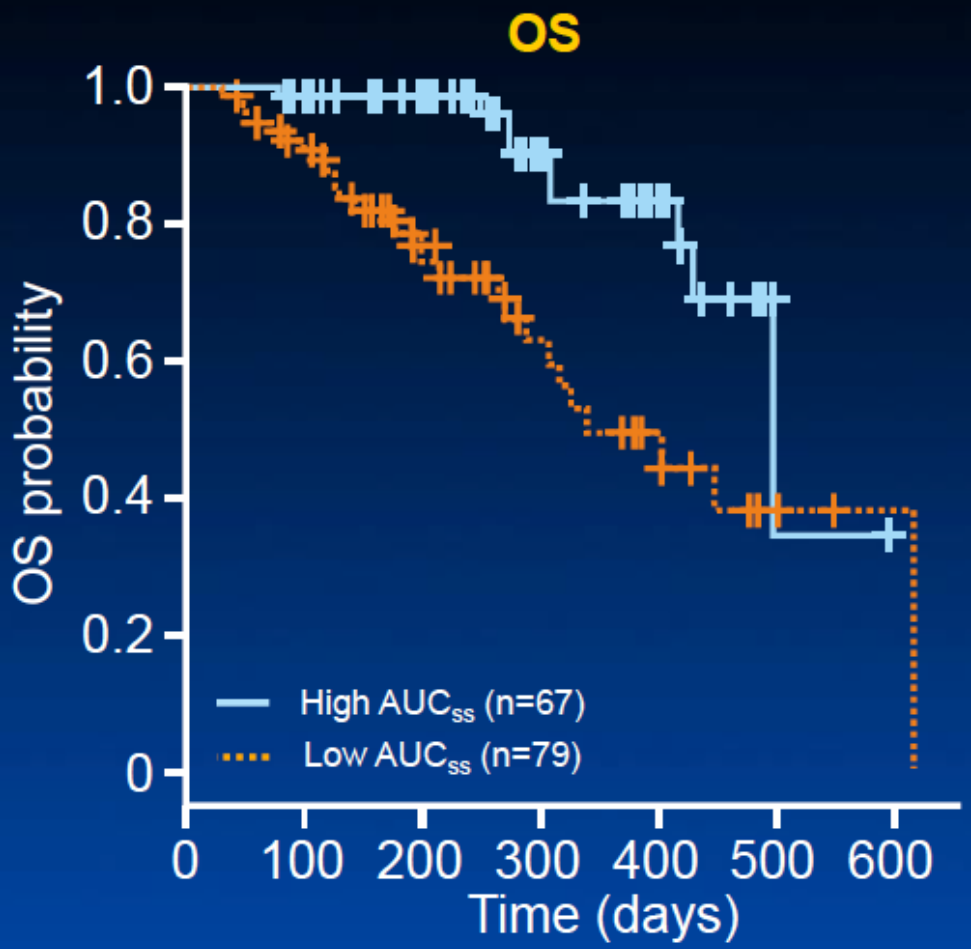
¿Todas la toxicidades tienen la misma relevancia?

- El oncólogo ha de distinguir entre las toxicidades que:
  - Tienen fácil manejo o producen molestias sin ser peligrosas
  - Requieren intervención médica
- El oncólogo ha de sopesar los efectos adversos y los beneficios del tratamiento y comunicárselo al paciente
- Algunas toxicidades no pueden privar al paciente de los tratamientos diana más beneficiosos

Mayor exposición SUNITINIB: Mejores resultados

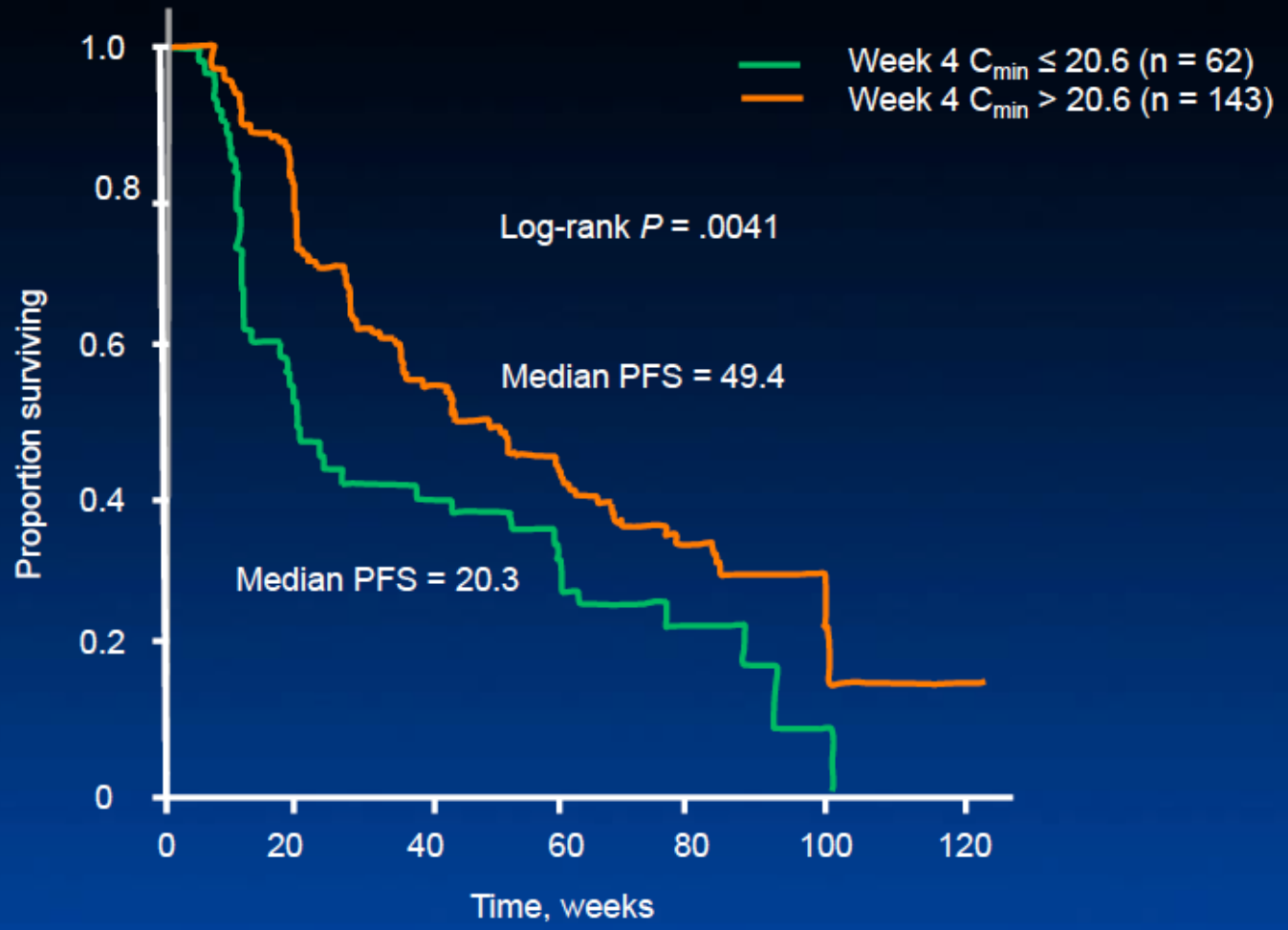
- Higher sunitinib exposure was associated with longer median time to tumour progression (TTP) and OS





Houk B, et al. *Cancer Chemother Pharmacol* 2010;66:357–71

Pazopanib: Mayor concentración plasmática (Cmin1) mejor Supervivencia Libre de Progresión



- Week 4 plasma pazopanib C_{min} >20.6 µg/mL was associated with significantly better PFS than C_{min} ≤20.6 µg/mL (p=0.0041)

1. Suttle *et al*. *J Clin Oncol* 2010; 28(Suppl): Abstract 3048 and poster.

¿Cómo pueden ser evitadas las reducciones de dosis y la interrupción de tratamientos?

- Con un manejo preventivo y adecuado de los efectos secundarios lo que incluye:
  - Educación al paciente
    - Información sobre los efectos secundarios y expectativas de eficacia del tratamiento
  - Soporte intensivo durante los 2-3 primeros ciclos
  - Medidas profilácticas
  - Manejo adecuado de los efectos secundarios cuando ocurren

Relevancia de cada cuadro

- Astenia
- Hipertensión
- Diarrea
- Hipotiroidismo
- Despigmentación piel y cabello
- Alteraciones metabólicas

- (Astenia)
- Estomatitis
- Síndr Mano-pie (HFS) Gr 2–3
- Trombocitopenia Gr 3-4
- Neutropenia Gr 4
- Toxicidades cardíacas
- Neumonitis intersticial
- Hipofosfatemia grave

Efectos secundarios que rara vez llevan a interrumpir o reducir de forma permanente las dosis de tratamiento con un manejo apropiado

Efectos secundarios que pueden llevar a una interrupción o reducción permanente de dosis

MANEJO de los FÁRMACOS ANTIDIANA en CÁNCER RENAL

Proyecto ProTECT-2
Prospective Toxicity Evaluation and Clinical managemenT-2

COORDINADORES: NURIA LAINEZ MILAGRO
JESÚS GARCÍA-DONAS JIMÉNEZ

SOGUG

HTA como marcador de actividad

Study	Disease	Anti-VEGF agent	HTA definition	Results
Rini et al.[1]	Multiple solid Tumors (n=230)	Axitinib	dBP ≥ 90 mmHg	OS: 30.1 vs.. 10.2 months (p<0.001) PFS: 13.1 vs. 5.8 months (p=0.1) ORR: 44% vs. 12% (p<0.001)
Rini et al.[2]	RCC (n=544)	Sunitinib	sBP > 140mmg and dBP ≥ 90 mmHg	OS: 30.9 vs. 7.2 months (p<0.0001) PFS: 12.5 vs. 2.5 months (p<0.0001) ORR: 55% vs. 9% (p<0.0001)
Harzstark et al.[3]	RCC (n=366)	Bevacizumab (+IFN)	≥ CTC Grade 2	OS: 41.6 vs.. 16.2 months (p<0.0001) PFS: 13.2 vs. 8.0 months (p=0.0009) ORR: 13% vs. 9% (p=ns)
Escudier et al.[4]	RCC (n=337)	Bevacizumab (+IFN)	≥ CTC Grade 2	PFS: 10.2 vs. 8.4 months (p=ns)

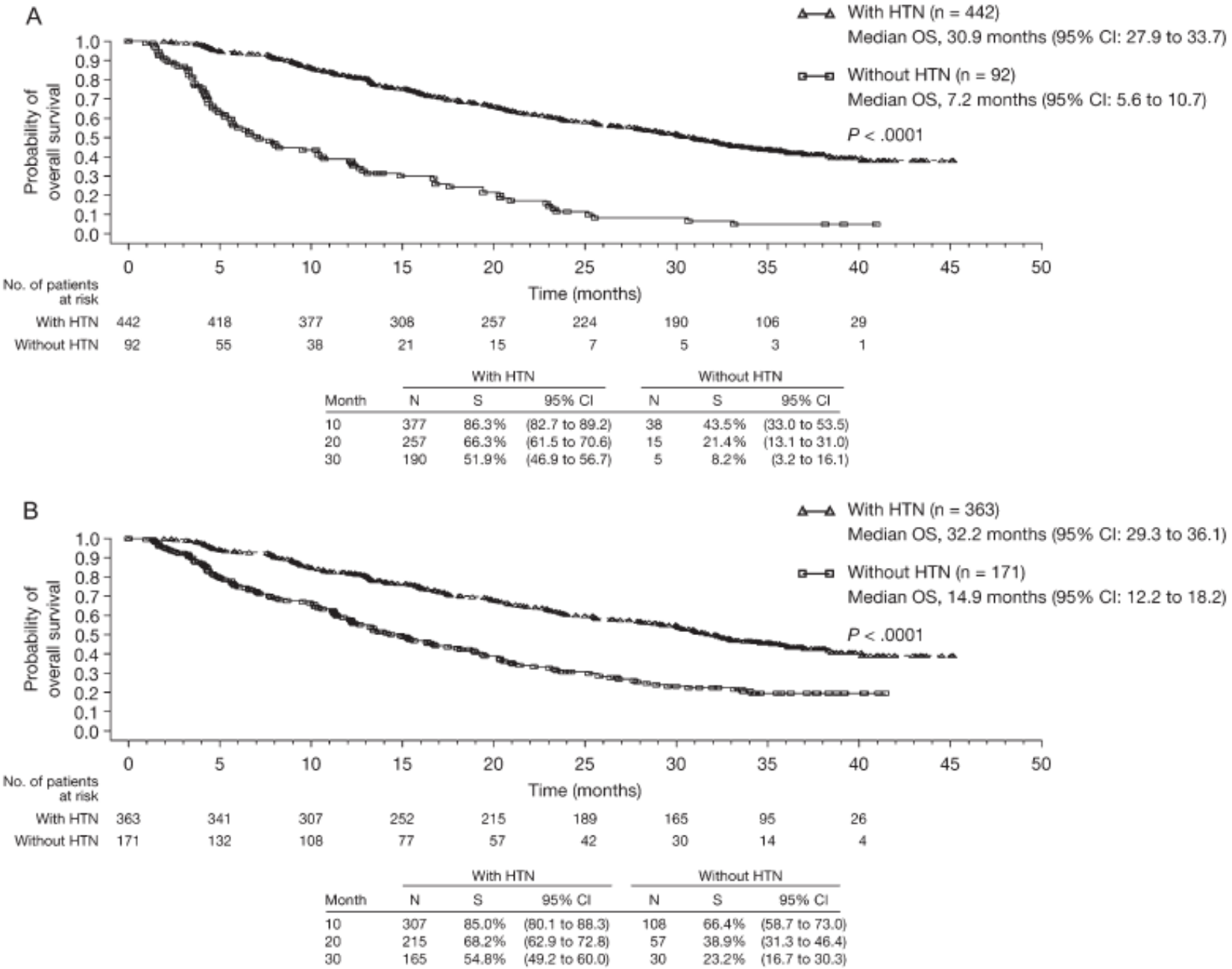


Figure 1. Kaplan–Meier estimates of overall survival (OS) by hypertension (HTN) status (post-cycle 1, day 1). In (**A**) HTN is defined by a maximum systolic blood pressure of at least 140 mm Hg. In (**B**), HTN is defined by a maximum diastolic blood pressure of at least 90 mm Hg. N = number at risk; S = survival percentage, with 95% confidence interval (CI) in parentheses.

Hipertensión Arterial (HTA)

- HTA Grado 1-4 ocurre en 26% y en el 10% de los casos es Grado 3-4
- Farmacos relacionados: Bevacizumab, Sunitinib, Axitinib, Sorafenib, Pazopanib

Antes del tratamiento

- Estabilizar la presión arterial con las medidas adecuadas

Durante el tratamiento

Objetivo mantener TA ≤ 140/90

- Vigilar frecuentemente la TA y tratar en caso necesario
  - Tratamiento individualizado (evitar diltiazem y verapamilo), monitorizar y valorar si precisa reducción dosis
- Se recomienda la suspensión temporal de sunitinib en pacientes con HTA severa que no se controla con manejo médico adecuado
  - El tratamiento se puede reiniciar una vez la TA está bien controlada

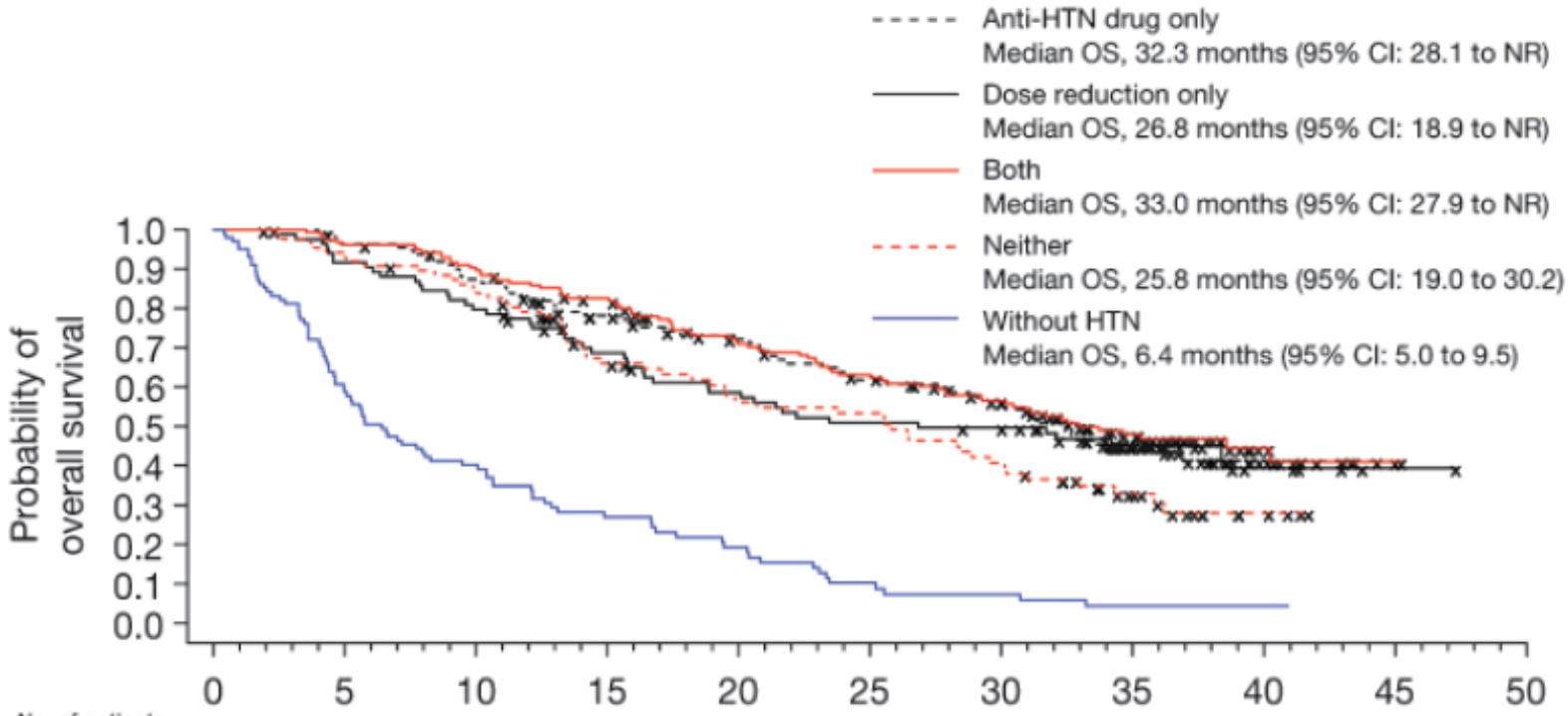
Ravaud A. Ann Oncol 2009 May;20 Suppl 1:i7-12.
Zhu X. Acta Oncologica,2009;48:9-17
Hutson TE, et al. Oncologist 2008;13:1084-96

Medicación anti hipertensiva durante el tratamiento con inhibidores de VEGF

Clase de Agente	Agente	Dosis Inicial	Dosis Máxima	Metabolismo Hepático
Bloqueantes cálcicos	Nifedipino XL	30 mg/d	90 mg/d	CYP 3A4
	Felodipino	2.5 mg/d	10 mg/d	CYP 3A4 (Inhibidor CYP 3A4)
	Amlodipino			
β Bloqueadores	Metoprolol	25 mg BID	100 mg BID	CYP 2D6
	Atenolol	25 mg/d	100 mg/d	None
Inhibidores ECA	Lisinopril	5 mg/d	40 mg/d	None
	Captopril	12.5 mg TID	50 mg TID	CYP 2D6
	Enalapril	5 mg/d	40 mg/d	CYP 3A4
ARBs	Candesartán	4 mg/d	32 mg/d	CYP 2C9
	Valsartan	80 mg/d	160 mg/d	Inhibits CYP 2C8/9 (weak)
	Losartán			
	Telmisartán	20mg/d		
α & β Bloqueantes	Carvedilol	6.25 mg BID	25 mg BID	CYP2C8/9 & CYP2D6
Vasodiladores	Minoxidil	5 mg/d	100 mg/d	Glucuronidación

J Clin Oncol 24: 1329, 2006

CONTRAINDICADOS: Verapamil y Diltiazem



No. of patients at risk									
Anti-HTN drug only	113	108	97	79	70	59	52	29	6
Dose reduction only	85	77	67	55	46	40	37	17	5
Both	157	151	140	125	101	87	72	44	14
Neither	87	82	73	49	40	38	29	16	4
Without HTN	92	55	38	21	15	7	5	3	1

	Anti-HTN drug only			Dose reduction only			Both		
Month	N	S	95% CI	N	S	95% CI	N	S	95% CI
10	97	87.4%	(83.8 to 93.6)	67	79.8%	(69.5 to 86.9)	140	89.7%	(83.8 to 93.6)
20	70	72.1%	(62.5 to 79.6)	46	58.6%	(47.1 to 68.4)	101	71.7%	(63.7 to 78.1)
30	52	55.3%	(45.1 to 64.4)	37	49.6%	(38.3 to 60.0)	72	56.4%	(48.0 to 64.1)

	Neither			Without HTN		
Month	N	S	95% CI	N	S	95% CI
10	73	85.0%	(75.5 to 91.0)	38	43.5%	(33.0 to 53.5)
20	40	56.2%	(44.4 to 66.4)	15	21.4%	(13.1 to 31.0)
30	29	40.7%	(30.0 to 51.6)	5	8.2%	(3.2 to 16.0)

J Natl Cancer Inst 2011;103:763-773

Sunitinib-associated hypertension was associated with improved clinical outcomes

These data support the hypothesis that hypertension may be a biomarker of efficacy

Improved clinical outcomes in patients with sunitinib-associated hypertension were independent of use of anti-hypertensive agents and hypertension-induced dose reductions

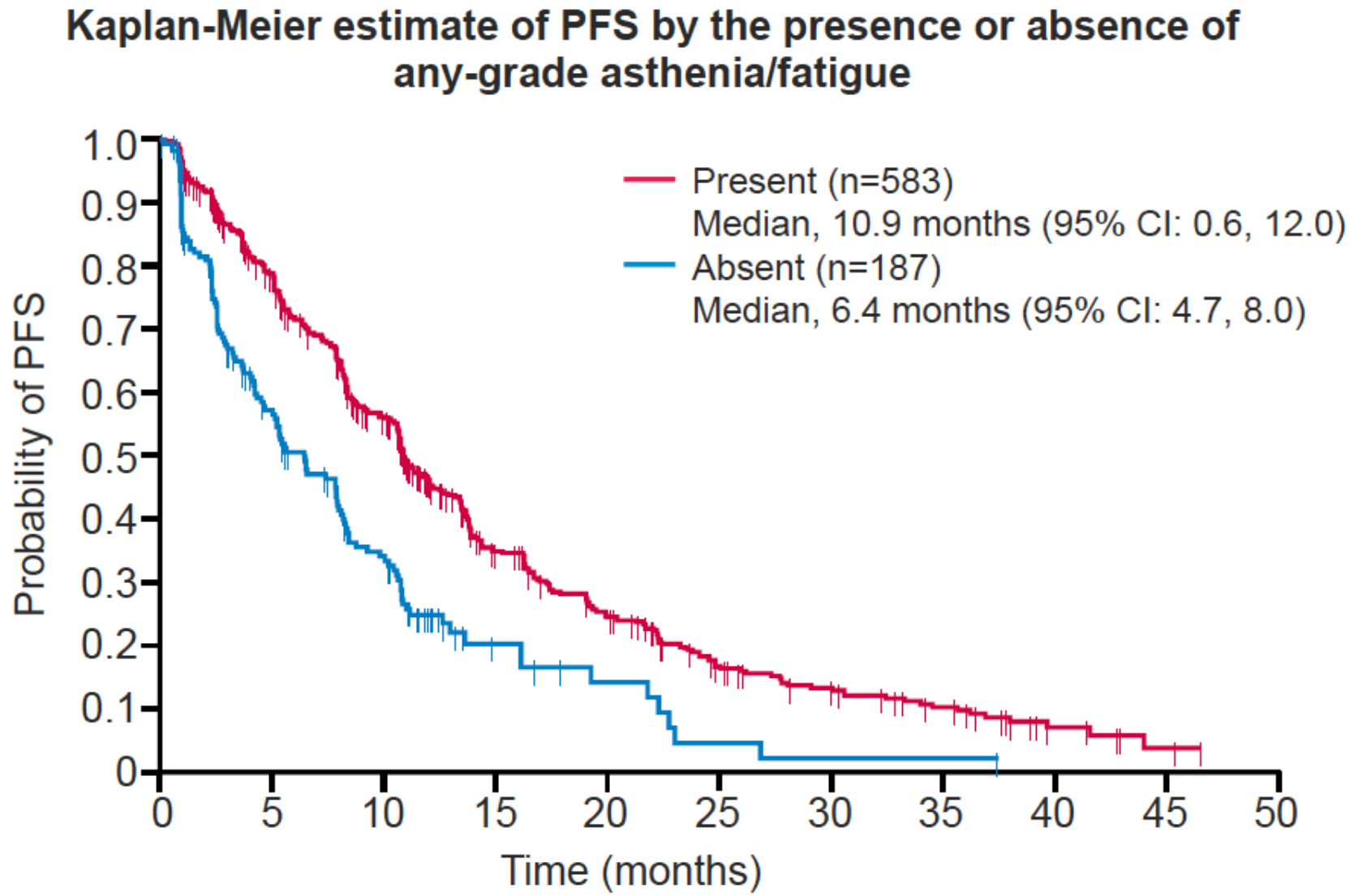
The incidence of hypertension-associated AEs was low, although patients with hypertension developed more renal toxicity than patients without hypertension ($p=0.013$)

The mechanism(s) underlying this phenomenon warrant further study

Hypertension should be monitored and treated appropriately in patients with mRCC receiving sunitinib

J Natl Cancer Inst 2011;103:763-773

Astenia/fatiga Biomarcador predictivo de eficacia en cáncer renal metástasico y Sunitinib



CI = Confidence interval

Davis et al ESMO 2011

Astenia

- Grado 1-4 en el 73% y Gr 3-4 en 18% de los pacientes
- Fármacos relacionados: Sunitinib, Bevacizumab, Sorafenib, Pazopanib, mTor

Antes del tratamiento

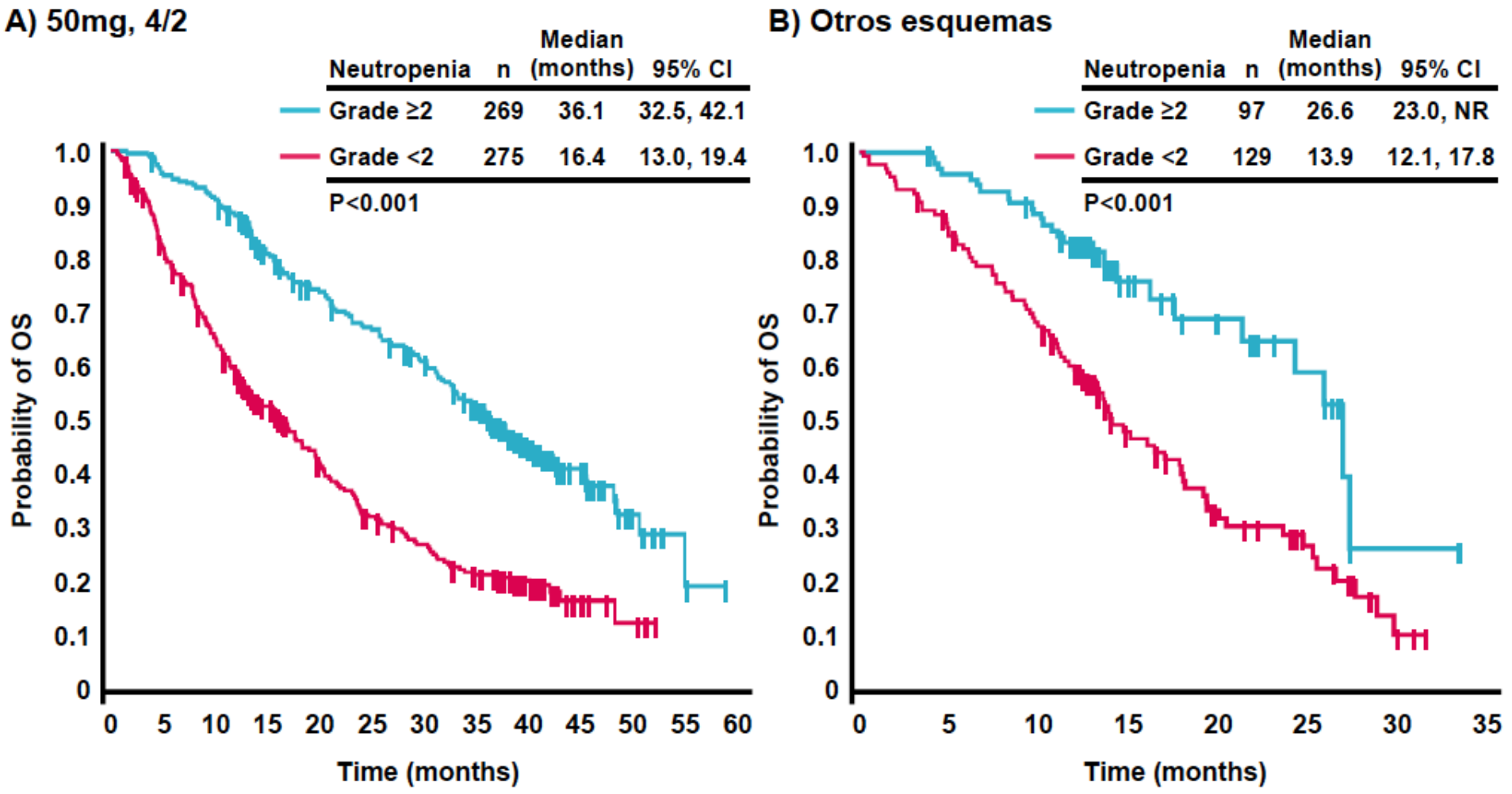
- Evaluar causas potenciales de astenia: depresión, trastornos del sueño, hipotiroidismo, anemia, hipofosfatemia
- Tratar estas causas según la práctica médica estándar

Durante el tratamiento

- Se ha de monitorizar a los pacientes regularmente
- Valorar signos de anemia, depresión e hipotiroidismo e iniciar el tratamiento apropiado
- Reforzar el valor de la terapia
- Si la calidad de vida se ve comprometida reducir la dosis

Kollmannsberger C, et al. Can Urol Asoc J 2007Jun 1,2 suppl: s41-54
Roigas J, Eur Urol Suppl 2008,7,593-600
Négrier S, Ravaud A. Eur J Cancer 2007 5,7 Suppl:12-19

Estimación SG por Kaplan–Meier en función del grado de Neutropenia



NR = not reached

Donskov et al ESMO 2011

Neutropenia grade ≥2 and thrombocytopenia grade >1 were associated with significantly longer TTP, PFS and OS in both KM and multivariate analyses

Correlation between neutropenia grade ≥2 and improved clinical outcome was observed irrespective of dosing or schedule

Development of neutropenia and thrombocytopenia during treatment may be previously unrecognised biomarkers of sunitinib efficacy in patients with mRCC

The results of these analyses also provided further validation for the use of baseline levels of neutrophils, thrombocytes and Hb as prognostic factors for survival in patients with mRCC (multivariate analysis)

Haematologic parameters should always be monitored closely during sunitinib treatment

Donskov et al. ESMO 2011.

Neutropenia

- Grado 1-4 en el 68% y Gr 3-4 en 20%
- Farmacos relacionados: Sunitinib, Bevacizumab, Sorafenib, Pazopanib

Antes del tratamiento

- Instruir al paciente con medidas que minimicen el riesgo de infección
- Realizar un hemograma antes de iniciar el tratamiento

Durante el tratamiento

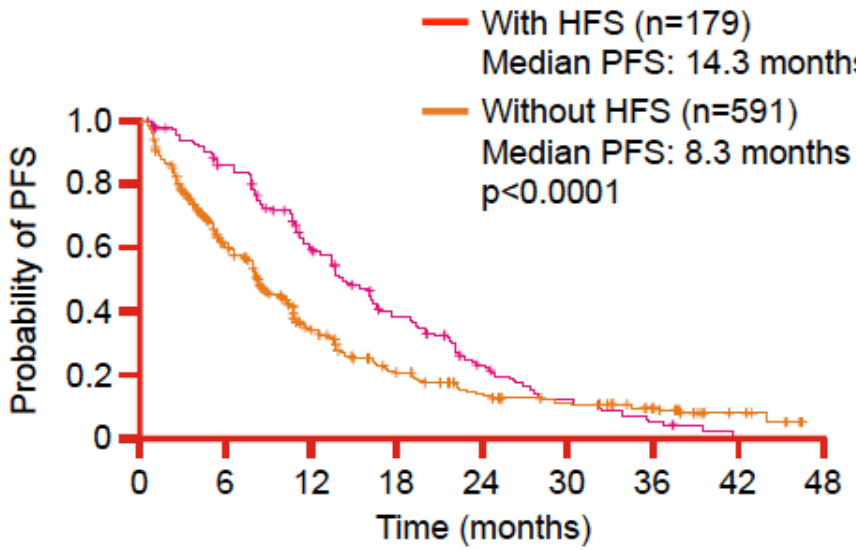
- Manejar la neutropenia de acuerdo con la práctica habitual
- Se ha de realizar un hemograma antes de cada ciclo
- Si se objetiva mielosupresión se ha de suspender el tratamiento y reiniciar cuando el recuento leucocitario se normalice
- La neutropenia no suele requerir modificación de dosis

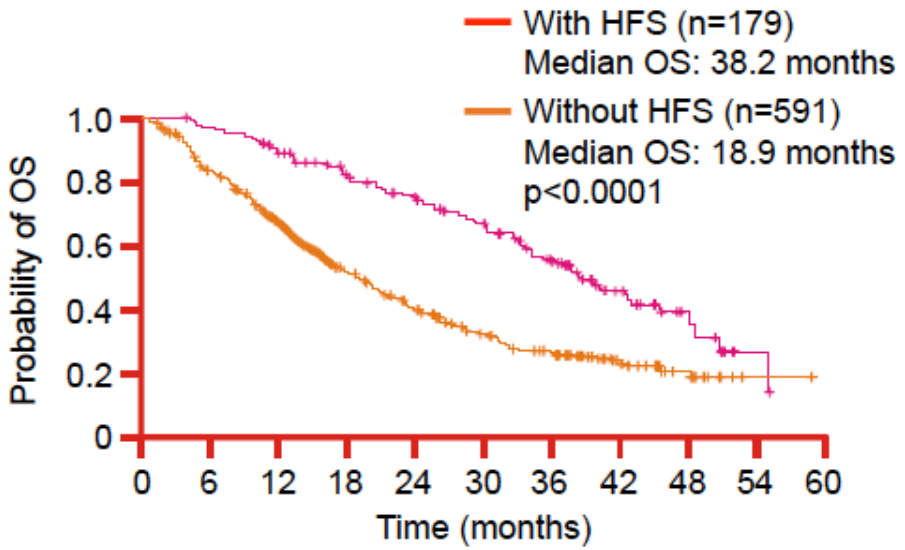
Kollmannsberger C, et al. Can Urol Asoc J 2007Jun 1,2 suppl: s41-54
Roigas J, Eur Urol Suppl 2008,7,593-600

Síndrome Mano pie (HFS) como biomarcador de eficacia al Sunitinib

- De 770 pacientes:
  - 179 (23%) desarrollaron cualquier grado de HFS
  - 591 (77%) no desarrollaron HFS

- En pacientes con SMP se asoció con una mejoría de SG y SLP





Michaelson et al ASCO GU 2011

Toxicidad Cutánea (S. Mano-pie; HFS)

- Grado 1-4 en el 27% y Grado 3-4 en 9% de pacientes
- Fármacos: Sorafenib, Sunitinib, Pazopanib, Everolimus y Temsirolimus

Antes del tratamiento

- Antes de iniciar el tratamiento realizar una buena exploración de los pies y descartar zonas de hiperqueratosis
- Educar a los pacientes sobre los potenciales efectos secundarios
- Medidas preventivas, consultar al podólogo si es preciso, evitar roces en manos, pies y otros puntos del cuerpo, cremas hidratantes

Durante el tratamiento

- Aconsejar al paciente usar calcetines y guantes de algodón y aplicar cremas con vit A y cremas de urea si son necesarias
- Consulta al dermatólogo si es preciso para tratar ampollas grado 2-3
- Reducir dosis o interrumpir el tratamiento cuando aparecen lesiones Grado ≥2 HFS hasta recuperación (Grado 0-1)
- Para el control del síndrome mano-pie se suelen utilizar más frecuentemente interrupciones que reducciones de dosis

Lacouture ME, et al. Oncologist 2008;13:1001-1011
Kollmannsberger C, et al. Can Urol Asoc J 2007Jun 1,2 suppl: s41-54
Roigas J, Eur Urol Suppl 2008,7,593-600

Sunitinib-associated HFS was a significant independent predictor of improved PFS and OS in patients with mRCC

The development of HFS may serve as a predictive biomarker of sunitinib efficacy in the treatment of mRCC

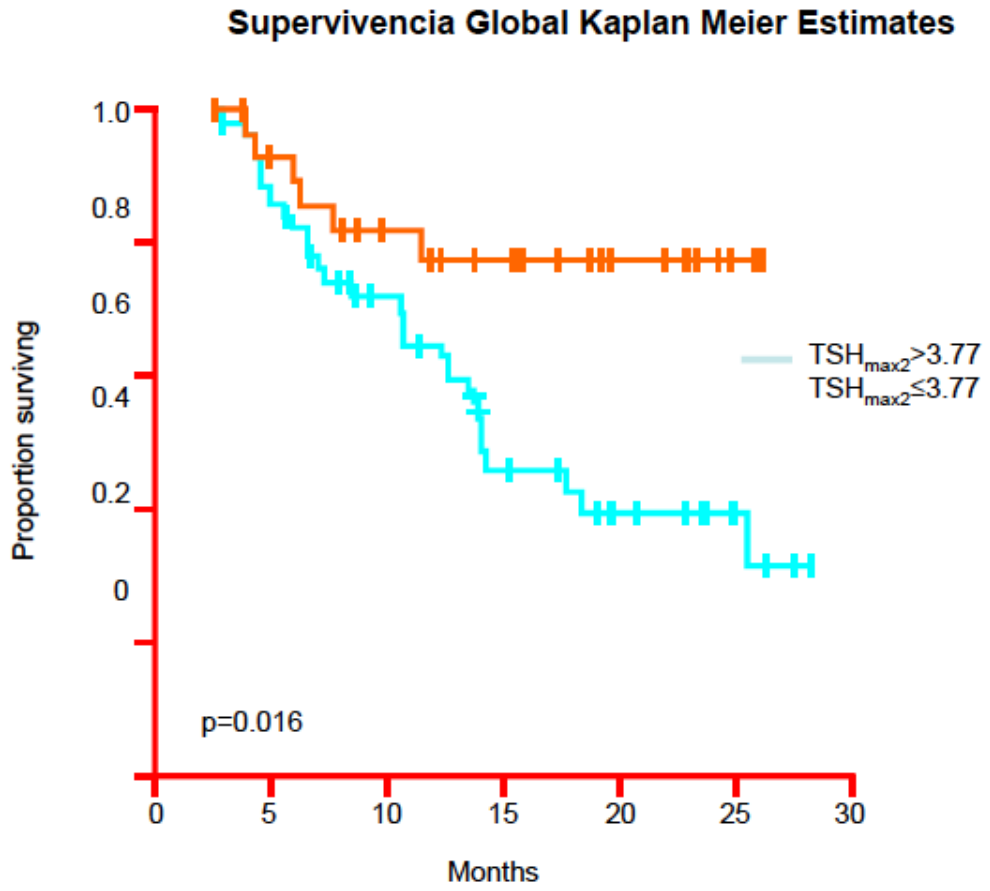
Landmark analysis demonstrated that HFS may more reliably predict OS than PFS at early timepoints

Although patients who did not develop HFS still had substantial benefit from sunitinib, the development of HFS identified a particularly favourable subset of patients

Pusanov. ESMO 2011

Hipotiroidismo valor predictivo de eficacia al Sunitinib

Pacientes tratados con sunitinib y sorafenib, n=87
Medida TSH cada 2 semanas



- Incremento de la TSH a los meses de tratamiento es un factor predictivo de supervivencia
  - HR: 0.35, p=0.016
- Mediana de supervivencia Global:
  - TSH > 3.77: n.r
  - TSH ≤ 3.77: 19.3 meses
- PFS:
  - TSH > 3.77: 17 meses
  - TSH ≤ 3.77: 10.8 meses
  - NS

TSH = thyroid-stimulating hormone; HR = hazard ratio

Schmidinger M, et al., *Cancer* 2010

Hipotiroidismo

- Grados 1-4 en un 24% y Gr 1-4 en el 1% de los pacientes
- Fármacos relacionados: Sunitinib, Sorafenib, Pazopanib, Axitinib

Antes del tratamiento

- Se recomienda valoración de función tiroidea pre-tratamiento
- Los pacientes con hipotiroidismo han de ser tratados de acuerdo a la práctica médica estándar

Durante el tratamiento

- Valorar regularmente los signos y síntomas de hipotiroidismo
- Los pacientes que presenten signos sugestivos de hipotiroidismo o TSH >10mU/L han de seguir monitorización y tratamiento estándar
- Se maneja bien con tratamiento hormonal teniendo como objetivo niveles de TSH de 0,5 a 2,5 mU/L

Kollmannsberger C, et al. Can Urol Asoc J 2007Jun 1,2 suppl: s41-54
Wolter P, et al. *Br J Cancer* 2008,99,448-454

Lainez et al. BMC Cancer (2016) 16:135
DOI 10.1186/s12885-016-2084-9

BMC Cancer

RESEARCH ARTICLE Open Access

Impact on clinical practice of the implementation of guidelines for the toxicity management of targeted therapies in kidney cancer. The protect-2 study

Nuria Lainez[1*†], Jesús García-Donas[2†], Emilio Esteban[3], Javier Puente[4], M. Isabel Sáez[5], Enrique Gallardo[6], Álvaro Pinto-Marín[7], Sergio Vázquez-Estévez[8], Luis León[9], Icíar García-Carbonero[10], Cristina Suárez-Rodríguez[11], Carmen Molins[12], Miguel A. Climent-Duran[13], Martín Lázaro-Quintela[14], Aranzazu González del Alba[15], María José Méndez-Vidal[16], Isabel Chirivella[17], Francisco J. Afonso[18], Marta López-Brea[19], Nuria Sala-González[20], Montserrat Domenech[21], Laura Basterretxea[22], Carmen Santander-Lobera[23], Irene Gil-Arnáiz[24], Ovidio Fernández[25], Cristina Caballero-Díaz[26], Begoña Mellado[27], David Marrupe[28], José García-Sánchez[29], Ricardo Sánchez-Escribano[30], Eva Fernández Parra[31], José C. Villa Guzmán[32], Esther Martínez-Ortega[33], María Belén González[34], Marina Morán[35], Beatriz Suarez-Paniagua[36], María J. Lecumberri[1] and Daniel Castellano[37]

Table 4 Reasons for non-compliance with SOGUG guidelines

	Sunitinib *718*	Sorafenib *227*	Pazopanib *142*	Everolimus *166*	Temsirolimus *100*	Bevacizumab *21*
Hypertension, n cycles (%)	374	227	73	–	–	3
Basal BP not recorded	–	226 (99.6)	27 (37.0)	–	–	3 (100)
BP not recorded	363 (97.1)	137 (60.4)	45 (61.6)	–	–	–
Dose reduction	9 (2.4)	–	1 (1.4)	–	–	–
Dose interruption	1 (0.3)	–	–	–	–	–
Treatment discontinuation	2 (0.5)	1 (0.4)	–	–	–	–
Cardiac toxicity, n cycles (%)	518	–	–	–	–	–
Non-recorded basal LVEF	145 (28.0)	–	–	–	–	–
LVEF not performed	484 (93.4)	–	–	–	–	–
Dose reduction	1 (0.2)	–	–	–	–	–
Dose interruption	1 (0.2)	–	–	–	–	–
Treatment discontinuation	2 (0.4)	–	–	–	–	–
Hypotyroidism, n cycles (%)	389	–	–	–	–	–
Basal TSH not recorded	114 (29.3)	–	–	–	–	–
TSH > 10 mU/l not-performed	358 (92.0)	–	–	–	–	–
Dose interruption	2 (0.5)	–	–	–	–	–
Diarrhea, n cycles (%)	180	31	36	–	–	–
Not recorded	165 (91.7)	29 (93.5)	36 (100)	–	–	–
Dose reduction	12 (6.7)	1 (3.2)	–	–	–	–
Dose interruption	3 (1.7)	1 (3.2)	–	–	–	–
Hyperglycemia, n cycles (%)	–	–	–	50	33	–
Not recorded	–	–	–	25 (100)	33 (100)	–
Dyslipemia, n cycles (%)	–	–	–	102	72	–
Not recorded	–	–	–	102 (100)	72 (100)	–
Pneumonitis, n cycles (%)	–	–	–	71	37	–
Basal data not recorded	–	–	–	66 (93.0)	35 (94.6)	–
Follow-up data not recorded	–	–	–	5 (7.0)	1 (2.7)	–
Treatment discontinuation	–	–	–	2 (2.8)	1 (2.7)	–
Liver toxicity, n cycles (%)	–	–	104	–	–	–
Basal liver function not recorded	–	–	19 (18.3)	–	–	–
Liver function not recorded	–	–	81 (77.9)	–	–	–
ALT increase > 3–8 ULN	–	–	5 (4.8)	–	–	–
Dose interruption	–	–	2 (1.9)	–	–	–
Treatment discontinuation	–	–	1 (1.0)	–	–	–
Proteinuria, n cycles (%)						
Not performed	–	–	–	–	–	19 (100)

Length of cycles according to routine clinical practice: sunitinib 6 weeks; other treatments 4 weeks

The most frequent reason for non-compliance with the Guidelines was the lack of test performing: basal and follow-up assessments of blood pressure, LVEF, TSH glucose, chest X rays, pulmonary function, DLCO and liver function were not performed as frequently as recommended by the Guidelines.

Inappropriate dose reductions, interruptions or treatment discontinuation were not reasons for non-compliance with Guidelines in the vast majority of non-compliant cycles.

BMC Cancer. 2016 Feb 22;16(1):135.

La intensidad de dosis y la duración del tratamiento son cruciales para conseguir los mejores resultados terapéuticos

La mayoría de los efectos secundarios no requieren reducción de dosis ni interrupciones

Manejar de forma activa los efectos que producen malestar para que los enfermos mantengan el cumplimiento del tratamiento

En todo momento se ha de sopesar el riesgo-beneficio del tratamiento

Biomarcadores

GROUP 1	GROUP 2	GROUP 3
Tumour tissue markers	**Circulating/blood markers**	**Clinical benefit/ surrogate endpoints**
• Fresh biopsy – Fine needle aspiration – Ascites • Paraffin embedded – Fresh – Archived	• Plasma – Circulating-free DNA • Serum • Circulating cells – Circulating tumour cells – Endothelial tumour cells	• Imaging: – DCE-MRI – DCE-ultrasound – CT – Functional imaging • Hypertension • Toxicities – Hypothyroidism – Skin changes

SULONG study

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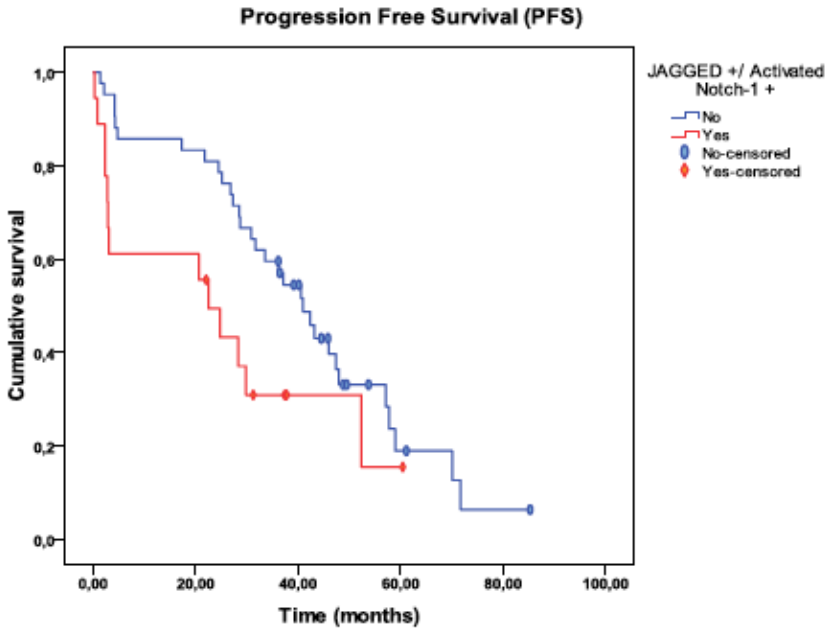
Baseline Patient characteristics N (%)		LR	PR	p-value
ECOG	ECOG 0	44 (55.0)	5 (23.8)	< 0.01
	ECOG 1	34 (42.5)	13 (61.9)	
	ECOG 2	0 (0)	3 (14.3)	
Nephrectomy	No, N (%)	2 (2.1)	4 (15.4)	< 0.01
	Yes, N (%)	94 (97.9)	22 (84.6)	
LDH (UI/L); Me.		258.41 CI _95% (235.86-280.96)	380.30 CI_95% (317.05-443.56)	< 0.001
Hemoglobin (g/dl); Me.		13.81 CI_95% (13.46-14.17)	11.96 CI_95% (11.07-12.86)	< 0.001
Platelets (/mm3); Me.		240.62 CI_95% (223.64-257.59)	368.63 CI_95% (303.66-433.59)	< 0.001
Time from diagnosis to treatment; Me., m.		47 CI_95% (36.56-57.45)	27.55 CI_95% (-1.29-56.40)	< 0.01
Metastasis at diagnosis	No, N (%)	63 (69.2)	12 (46.2)	< 0.05
	Yes, N (%)	28 (30.8)	14 (53.8)	
Lung metastasis		59 (60.8)	23 (88.5)	< 0.01
Brain metastasis		3 (3.1)	4 (15.4)	< 0.05
Hepatic metastasis		7 (7.2)	6 (23.1)	< 0.05
Fuhrman grade	Grade 1	7 (10.3)	0 (0)	< 0.05
	Grade 2	21 (30.9)	4 (23.5)	
	Grade 3	30 (44.1)	5 (29.4)	
	Grade 4	10 (14.7)	8 (47.1)	

SULONG study



- Our results are suggesting that **Notch signaling activation (Jagged-1/N1ICD+ staning) predicts poor outcome in metastatic ccRCC (TNM IV) and may identify pts who show drug resistance.**

- Notch signaling activation was associated to **adverse pathological features**: higher Furhman grade and metastasis at diagnoses.

- Shh pathway seems to be also activated in metastatic CCRCC and their signaling activation seems to predict shorter PFS.

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Single nucleotide polymorphism associations with response and toxic effects in patients with advanced renal-cell carcinoma treated with first-line sunitinib: a multicentre, observational, prospective study

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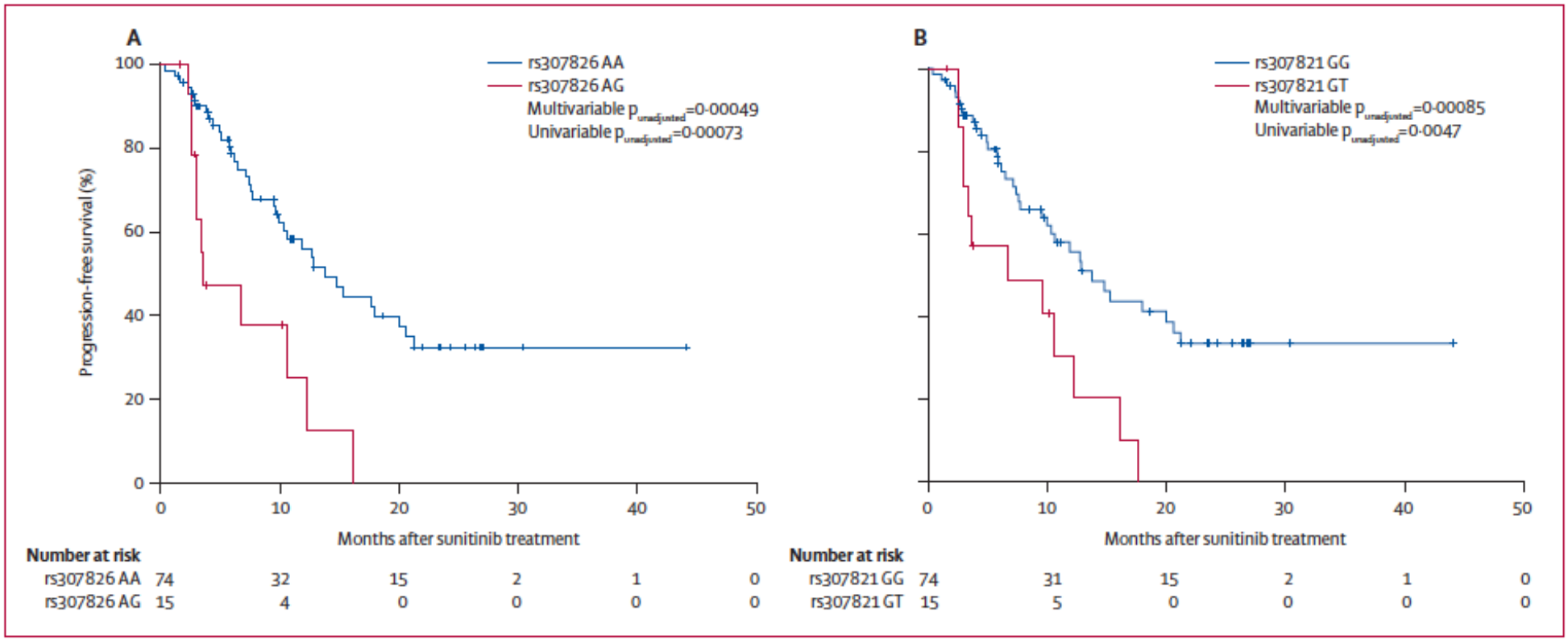

Figure 1: **Kaplan-Meier analysis of progression-free survival in patients with the rs307826 and rs307821 variants in *VEGFR3* with renal cancer after treatment with sunitinib**
(A) Patients grouped according to rs307826; median progression-free survival for wild type (AA) was 13·7 months (95% CI 9·7–17·7) and heterozygous (AG) was 3·6 months (0·0–8·7). (B) Patients grouped according to rs307821; median progression-free survival for wild type (GG) was 13·7 months (9·8–17·6) and heterozygous (GT) was 6·7 months (0·0–16·6). p values are from unadjusted multivariable analysis and from the unadjusted univariable log-rank test.

Lancet Oncol 2011;12:1143-50

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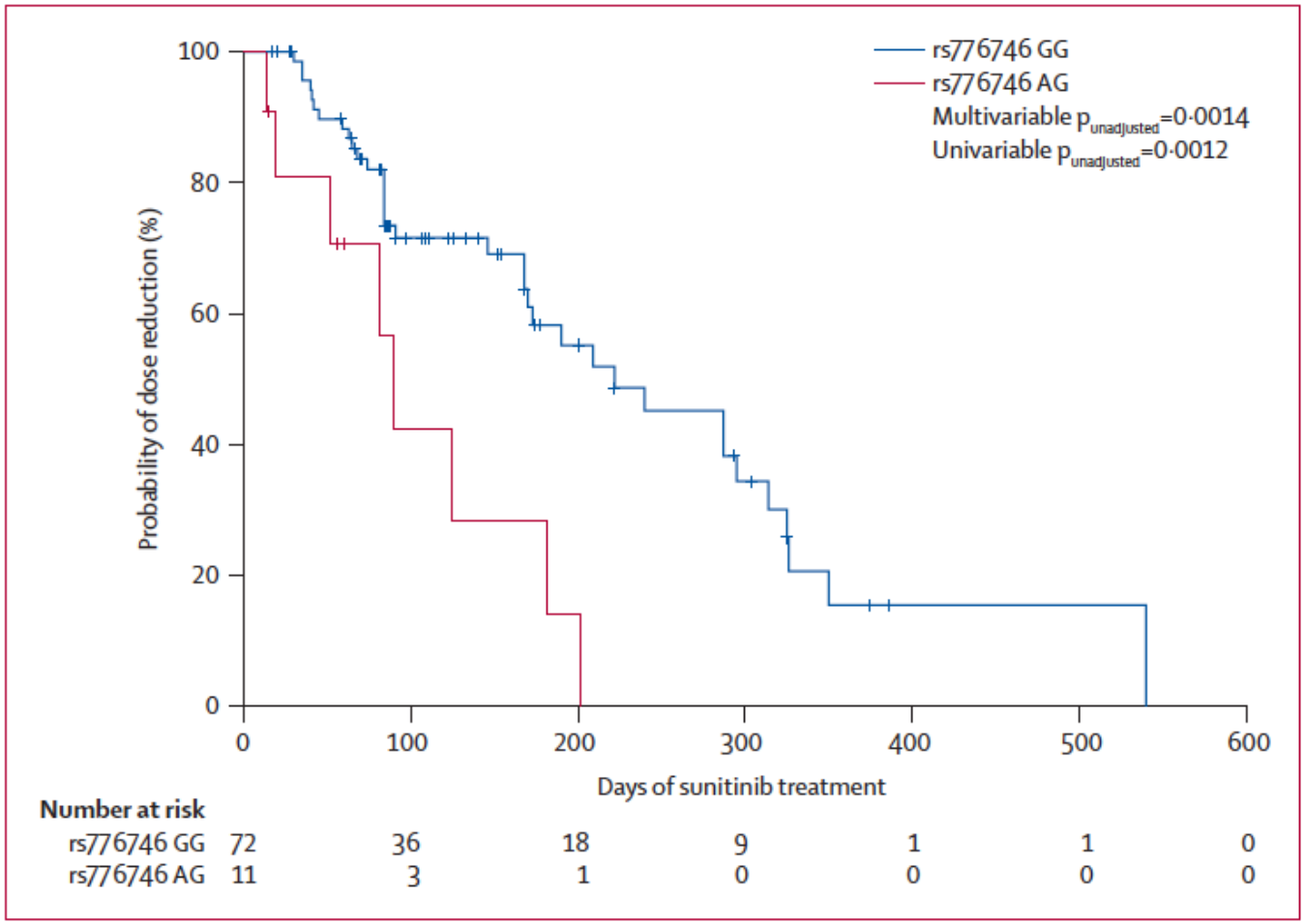

Figure 2: **Kaplan-Meier analysis of time on sunitinib treatment until dose reduction because of toxic effects for patients with the rs776746 variant in *CYP3A5***

84 patients included in the analysis had an initial sunitinib dose of 50 mg on a 4 weeks on, 2 weeks off schedule. One patient did not have genotype data for this single nucleotide polymorphism.

Lancet Oncol 2011;12:1143-50

SOG-ANG-2013-01	Multicentric and prospective epidemiological study to identify prognostic and predictive biomarkers of response to antiangiogenic drugs approved in first line of treatment for advanced or metastatic renal cell carcinoma	Dr. Emilio Esteban