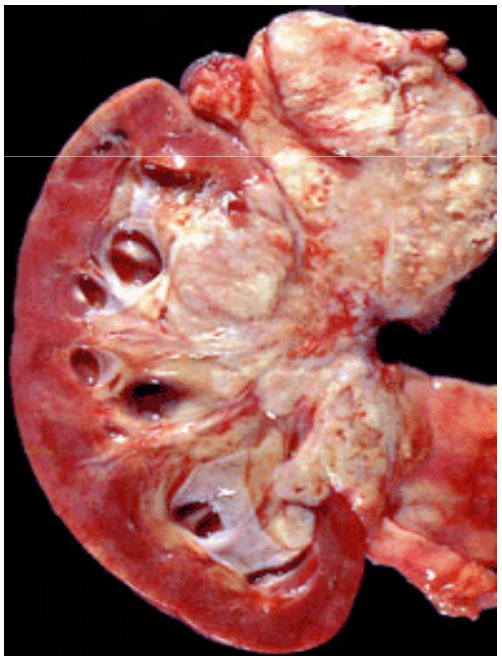
RAFAŁ STEC

Personalizing treatment of kidney cancer (renal cell carcinoma) based on the current opportunities and new strategies



Poznań, 14 Mar 2019 r.

Disclosure declaration

Grant/Research Support: ***Angellini.***

Honorary speakers: ***Angellini, Amgen, Novartis, Pfizer.***

Consultant: ***Amgen, Novartis, Roche.***

Renal cell carcinoma
EPIDEMIOLOGY in Poland

- **1.9% of all cancer cases worldwide**
- **National Cancer Registry Data 2016 (recent):**

- number of new cases per year: 3,134 men and 2,000 women

- number of deaths per year: 1,682 men and 955 woman

- **Standing increasing rates of 2-3%/year**
- **30% of patients have distant metastases at initial diagnosis**
- **And next 50%, within 3 years**

Personalized medicine/healthcare – the most important ”step” to achieve the our goal

- **Personalized medicine/healthcare is associated with the adaptation of the therapeutic procedure and methods of prevention to each patient. An individual approach increases the effectiveness, efficiency and safety of the therapy and the chance of complete cure.**

Personalization - treatment of kidney cancer

- **Step 1.Staging the disease.**
- **Step 2. The prognostic group of patients.**
- **Step 3. Factors that are related to the patient.**
- **Step 4. Potential biomarkers that are related to cancer.**
- **Step 5. Patient’s choice.**

Step 1.

Staging the disease.

Potential Methods of Treatment Kidney Cancer

1. Surgical treatment

- radical nephrectomy / nephron–sparing surgery (NSS)

- metastasectomy

2. Radiotherapy

3. Systemic treatment

- immunotherapy 👆

- molecular-targeted treatment 👆

Surgical treatment

Nephrectomy should be performed on patients even in the case of metastatic disease (unless there are contraindications):

total nephrectomy or nephron–sparing surgery (NSS)

Surgical treatment

Metastasectomy, even in the case of advanced kidney cancer which can prolong survival:

- resection of single metastases

- **metastasectomy of numerous metastases to lungs, liver and other organs, but "radical", not cytoreduction**

Radiotherapy in the treatment of RCC

Radiotherapy in RCC:

- irradiation of CNS metastases

- irradiation of skeletal metastases

Systemic treatment

The importance of choosing the 1st line of treatment

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journal homepage: www.ejcancer.info

Second line treatment of metastatic renal cell carcinoma: The Institut Gustave Roussy experience with targeted therapies in 251 consecutive patients

Antonin Levy, Jean Menard, Laurence Albiges, Yohann Loriot, Mario Di Palma, Karim Fizazi, Bernard Escudier *

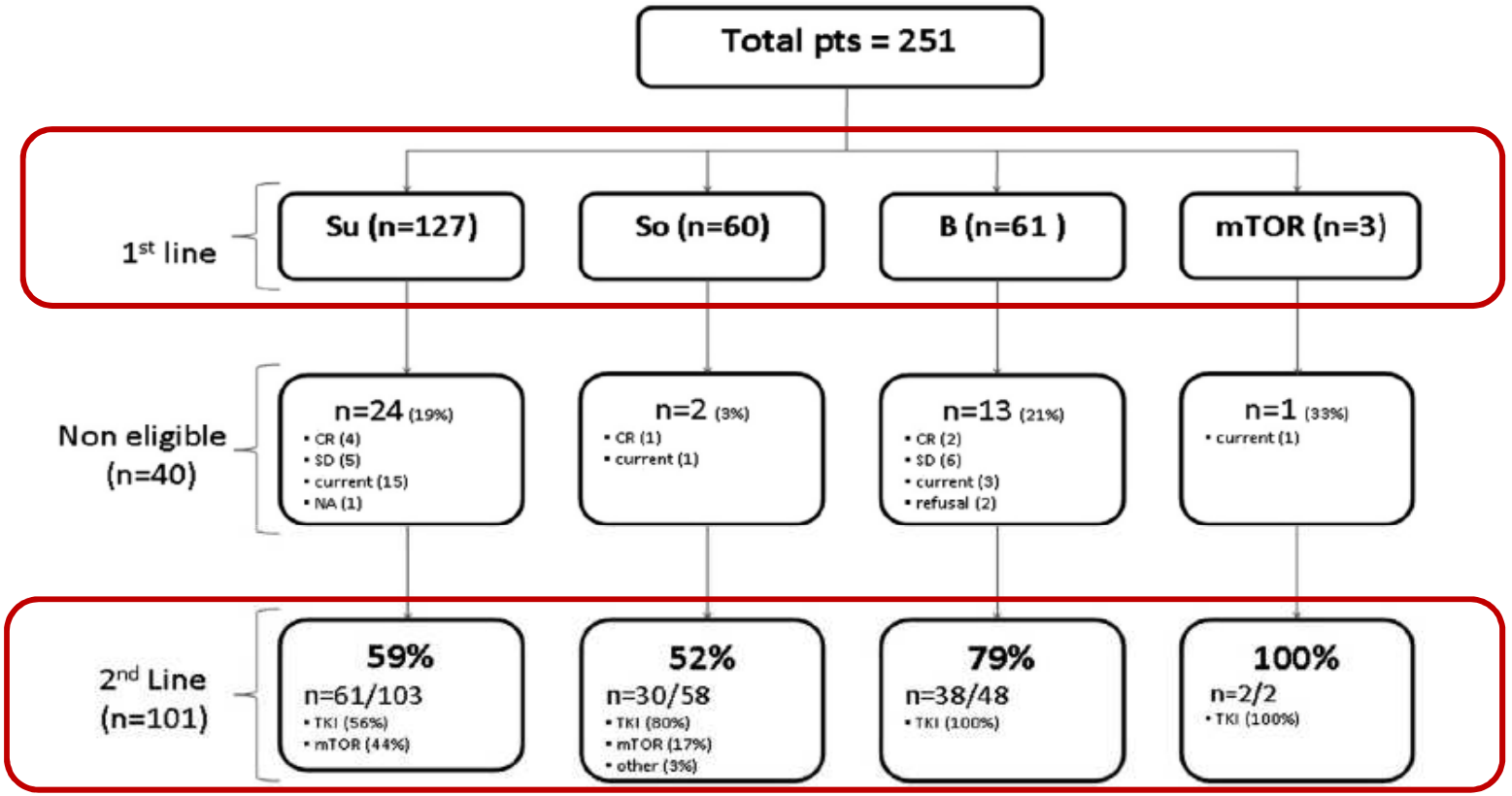


Fig. 1. Percentage of patients receiving a second line of treatment.

3.3. Second and third line exposure

Overall, 131 patients received a second line (131/251, 52.2%). According to our definition, 62% of 211 'eligible' patients received a second line with noticeable differences according to first line treatment: 59% ($n = 61/103$) for SU, 52% ($n = 30/58$) for SO and 79% ($n = 38/48$) for B (Fig. 1). The frequency of use of a second line treatment based on MSKCC classification and Eastern Cooperative Oncology Group (ECOG) performance status score (PS) is summarised Table 2. MSKCC classification ($P = 0.02$) and first line agent ($P = 0.001$) were significantly predictive for receiving a second line of treatment. PS score was not significantly predictive for receiving second line treatment (Table 2).

Forty-seven patients received third line treatment according to the eligibility criteria (47/131, 36%). The percentage of patients who received a third line according to the first line agent were: 56% (27/48), 28% (7/25) and 65% (13/20) for SU, SO and B respectively.

Original Study

Fuhrman Grade and Neutrophil-To-Lymphocyte Ratio Influence on Survival in Patients With Metastatic Renal Cell Carcinoma Treated With First-Line Tyrosine Kinase Inhibitors

Pawel Chrom,[1] Rafal Stec,[1] Aleksandra Semeniuk-Wojtas,[1] Lubomir Bodnar,[1] Nathaniel J. Spencer,[2] Cezary Szczylik[1]

Table 1 Patient Characteristics (n = 266)

Variable	n (%)
Age at start of TKI therapy (years)	
Median	61
Range	22-85
Interval from diagnosis to TKI therapy (mo)	
Median	13.3
Range	0-242
Male gender	180 (67.7)
ECOG PS	
0	117 (44.0)
1	143 (53.7)
2	6 (2.3)
Histologic type	
Clear cell	248 (93.2)
Other	19 (6.8)
Sarcomatoid features	16 (6.0)
Fuhrman grade[a]	
1	13 (5.4)
2	127 (53.2)
3	71 (29.7)
4	28 (11.7)
TNM T stage[b]	
T1	45 (19.5)
T2	68 (29.6)
T3	109 (47.4)
T4	8 (3.5)
Previous immunotherapy	29 (10.9)
First-line TKI treatment	
Sunitinib	201 (75.6)
Pazopanib	45 (16.9)
Sorafenib	20 (7.5)
Second-line treatment	
None	159 (59.8)
Everolimus	97 (36.4)
Axitinib	10 (3.8)
Metastatic sites	
1	54 (20.3)
2	76 (28.6)
>2	136 (51.1)

Step 2. The prognostic group of patients.

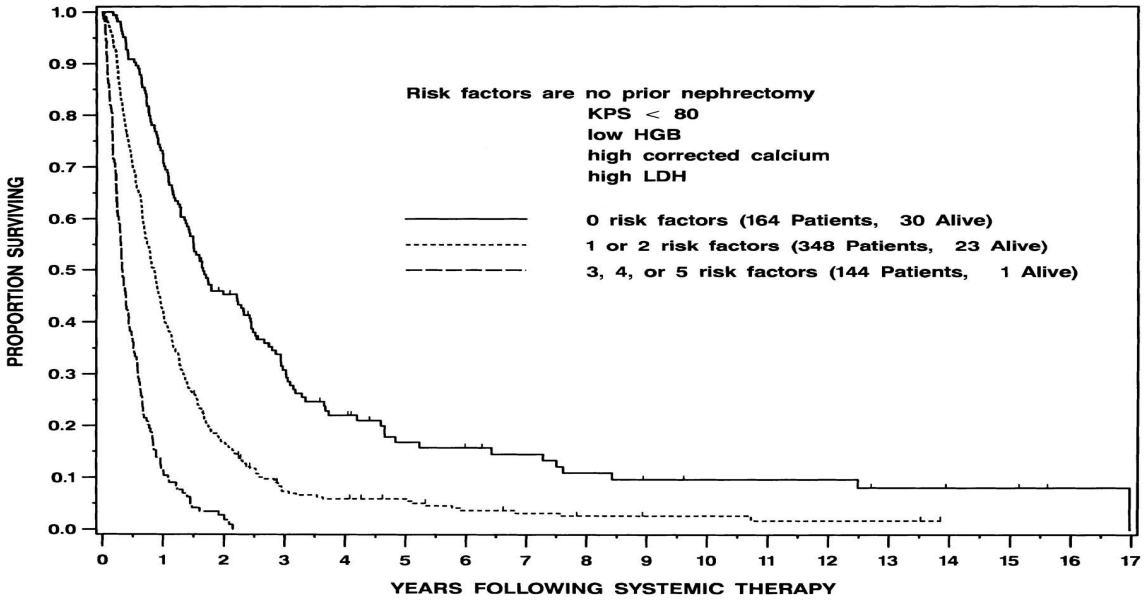
«Ideal» Prognostic scale

- **Easy to use**
- **Correctly identifies groups of patients with different results**
- **Useful in informing patients**
- **Useful for making a therapeutic decision**

Prognostic scale: MSKCC

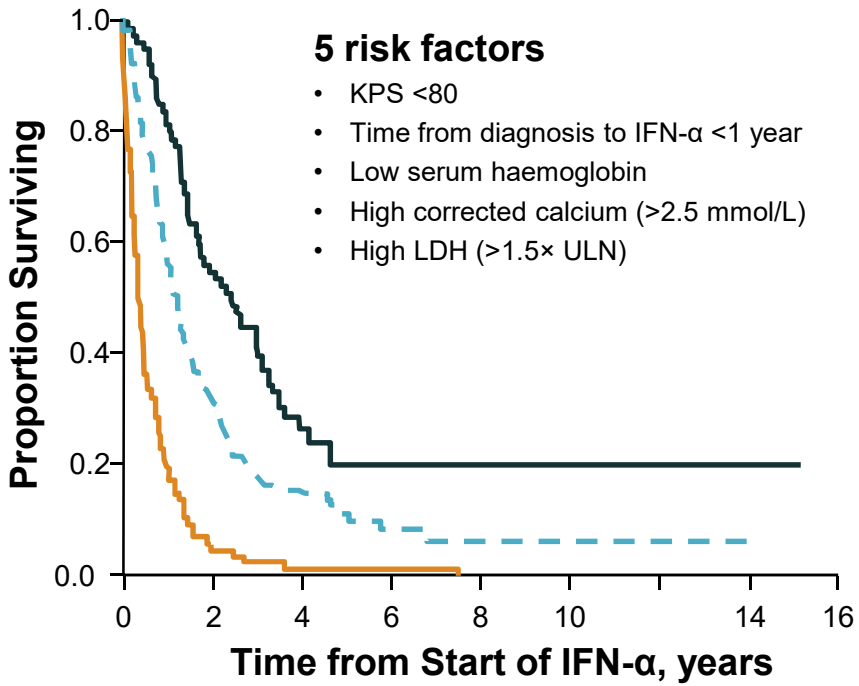
(Memorial Sloan Kettering Cancer Center)

N= 670



Motzer et al. J Clin Oncol. 1999

N= 463



Motzer et al. J Clin Oncol. 2002

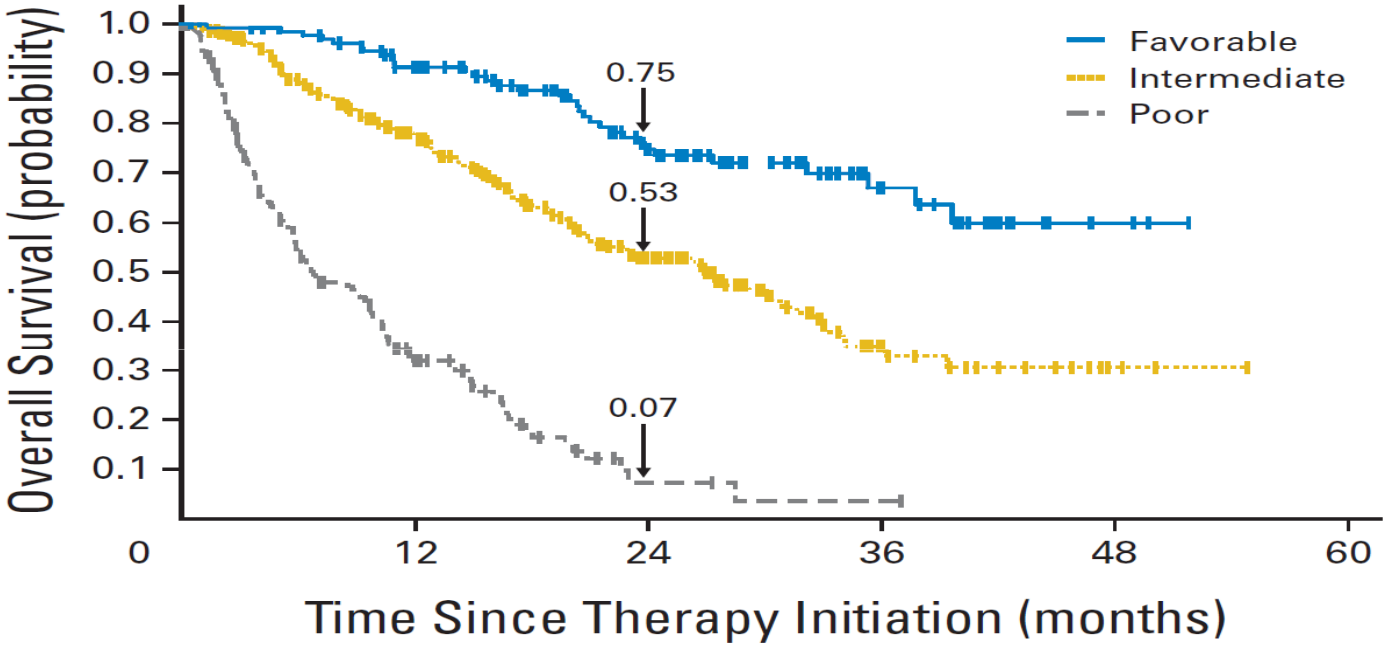
Prognostic scale: Heng's criteria (IMDC)

(The International Metastatic Renal Cell Carcinoma Database Consortium)

Parameter	Parameter Estimate ± SE	Hazard Ratio	95% CI	*P*
Clinical				
KPS < 80%	0.92 ± 0.14	2.51	1.92 to 3.29	< .0001
Time from diagnosis to treatment < 1 year	0.35 ± 0.13	1.42	1.09 to 1.84	.0098
Laboratory				
Hemoglobin < LLN	0.54 ± 0.14	1.72	1.31 to 2.26	.0001
Calcium > ULN	0.59 ± 0.17	1.81	1.29 to 2.53	.0006
Neutrophil count > ULN	0.88 ± 0.17	2.42	1.72 to 3.39	< .0001
Platelet count > ULN	0.40 ± 0.16	1.49	1.09 to 2.03	.0121

Heng et al. J Clin Oncol. 2009

Prognostic scale: **Heng's criteria** (IMDC)



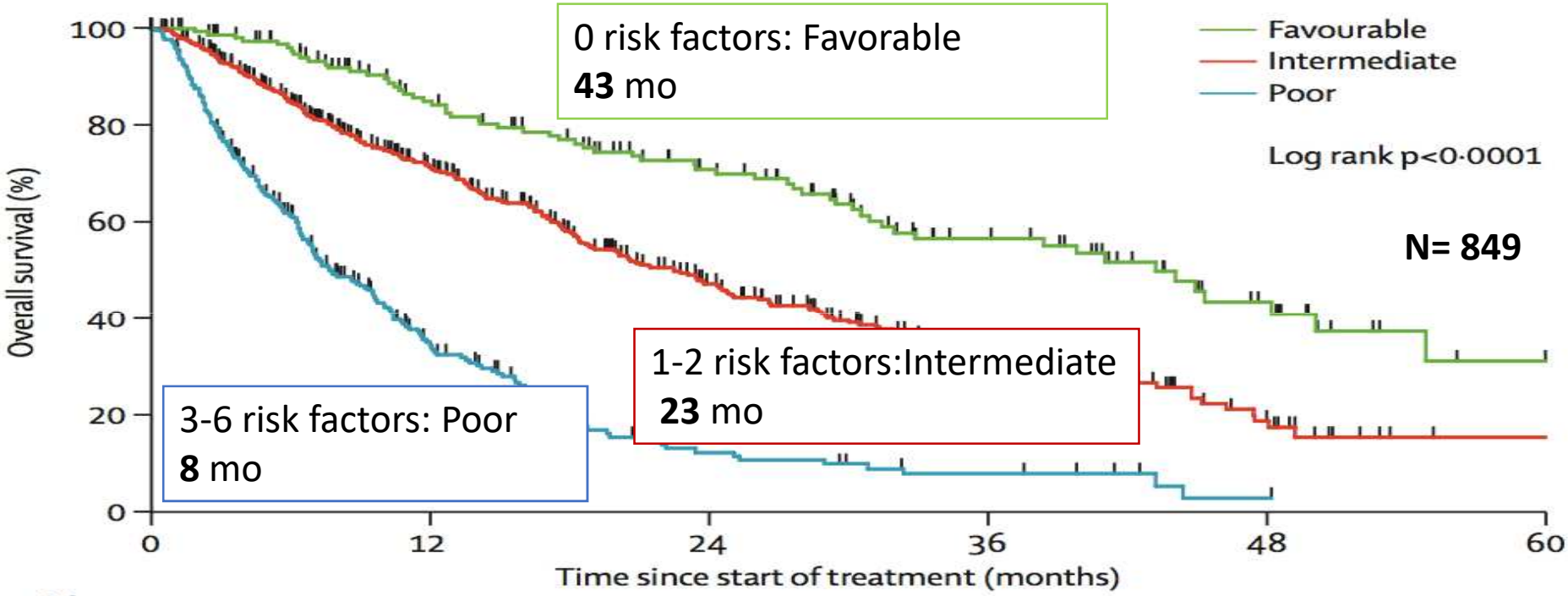
0 risk factors
1 – 2 risk factors
3 – 6 risk factors

N= 645

No. of events/No. at risk					
Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

Heng et al. J Clin Oncol. 2009

Prognostic scale: Heng's criteria (IMDC)



Number at risk

Favourable	157	109	74	40	17	3
Intermediate	440	247	122	59	15	1
Poor	252	65	15	7	1	0

Heng et al. Lancet Oncol. 2013

Parameters of different models

	Risk Factors Assessed	MSKCC Model	French Model	CCF Model	IKCWG Model	CCF Model (2)	IMDC Model
Clinical	**KPS or ECOG PS**	√	√		√	√	√
Clinical	**Time from diagnosis to treatment**	√		√	√	√	√
Clinical	Time from diagnosis to metastasis		√				
Clinical	Previous immunoTx or RTx			√ (RTx)	√ (ImmunoTx)		
Clinical	Number of metastatic sites		√	√	√		
Clinical	Liver metastasis		√				
Biological	Haemoglobin concentration	√		√	√		√
Biological	**Calcium concentration**	√		√	√	√	√
Biological	Neutrophil count					√	√
Biological	Platelet count					√	√
Biological	LDH concentration	√		√	√		
Biological	White blood cell count				√		
Biological	Alkaline phosphatase				√		

Table modified from Heng et al. Lancet Oncol. 2013

Motzer RJ et al. J *Clin Oncol.* 2002;20:289-296;Negrier S et al. *Ann Oncol.* 2002;13:1460-1468; Mekhail T et al. *J Clin Oncol.* 2005;23:832-841; Manola J et al. *Clin Cancer Res.* 2011;17:5443-5450.; Choueiri TK et al. *Cancer.* 2007;110:543-550.; Heng DY et al. *J Clin Oncol.* 2009;27:5794-5799.

1st line treatment of metastatic renal cell carcinoma/Poland/favourable and intermediate group

European Journal of Cancer 65 (2016) 102–108

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

First-line sunitinib versus pazopanib in metastatic renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium

Jose Manuel Ruiz-Morales [a,b], Marcin Swierkowski [c], J. Connor Wells [a], Anna Paola Fraccon [d], Felice Pasini [e], Frede Donskov [f], Georg A. Bjarnason [g], Jae-Lyun Lee [h], Hao-Wen Sim [i], Andrzej Sliwczynsk [j], Aneta Ptak-Chmielewska [k], Zbigniew Teter [l], Benoit Beuselinck [m], Lori A. Wood [n], Takeshi Yuasa [o], Carmel Pezaro [p], Brian I. Rini [q], Cezary Szczylik [c], Toni K. Choueiri [r], Daniel Y.C. Heng [a,*]

[c] *Department of Oncology, Military Institute of Medicine, Warsaw, Poland*

The number of patients enrolled in clinical practice - 1st line treatment

- **Sunitinib: 6,519 patients**
- **Pazopanib: 919 patients**
- **Median follow-up: 40.4 months**

Table 1
Baseline characteristics.

	SU	PZ	
Median age	62 (IQR: 56–69)	65 (IQR: 58–73)	$p < 0.0001$
KPS <80%	816/6084 (13%)	122/879 (14%)	$p = 0.70$
Diagnosis to treatment <1 year	3569/6517 (55%)	470/918 (51%)	$p = 0.04$
Hypercalcaemia	738/5860 (13%)	110/833 (13%)	$p = 0.62$
Low haemoglobin	2805/6223 (45%)	386/876 (44%)	$p = 0.57$
Neutrophilia	821/6122 (13%)	102/870 (12%)	$p = 0.17$
Thrombocytosis	919/6140 (15%)	129/884 (15%)	$p = 0.77$
Male	4630/6519 (71%)	646/919 (70%)	$p = 0.65$
Nephrectomy	5627/6514 (86%)	811/917 (88%)	$p = 0.09$
Heng – IMDC risk group (n = 2830)	Favourable 1259/5514 (23%)	197/807 (24%)	$p = 0.36$
	Intermediate 3175/5514 (57%)	467/807 (58%)	
	Poor 1080/5514 (20%)	143/807 (18%)	
Liver metastases	812/4038 (20%)	71/487 (15%)	$p = 0.004$
Brain metastases	344/4108 (8%)	34/479 (7%)	$p = 0.34$
Non-clear cell	374/3863 (10%)	29/417 (7%)	$p = 0.07$
Greater than one site of metastases	3200/4269 (75%)	388/504 (77%)	$p = 0.32$
Prior immunotherapy	664/6501 (10%)	97/908 (11%)	$p = 0.66$
Patients still on first-line TKI	1345/6510 (21%)	353/917 (39%)	$p < 0.0001$
Second line	2667/6519 (41%)	290/919 (32%)	$p < 0.0001$[a]
Sorafenib	585/2667 (22%)	6/290 (2%)	
Axitinib	225/2667 (8%)	57/290 (20%)	
Everolimus	1194/2667 (45%)	154/290 (53%)	
Other	673/2667 (25%)	73/290 (25%)	
Third line	980/3917[b] (25%)	82/510[b] (16%)	$p = 0.0007$[a]
Sorafenib	204/980 (21%)	8/82 (10%)	
Axitinib	81/980 (8%)	18/82 (22%)	
Everolimus	283/980 (29%)	29/82 (35%)	
Other	412/980 (42%)	27/82 (33%)	

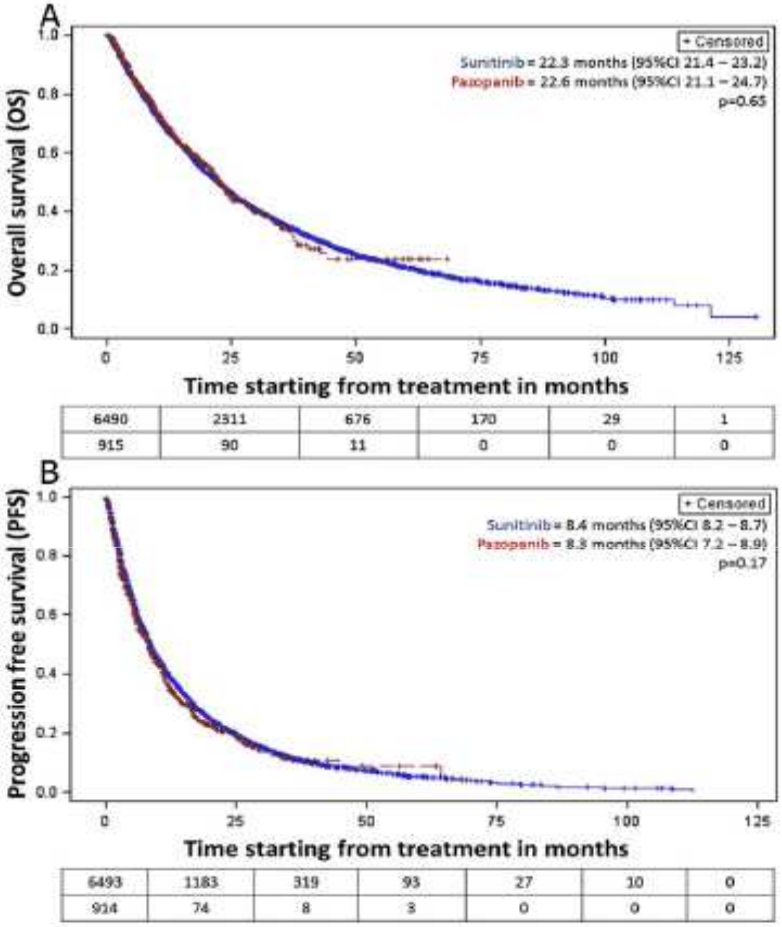


Fig. 1. (A) Overall survival of first-line sunitinib (SU) versus pazopanib (PZ). (B) Progression-free survival of first-line SU versus PZ.

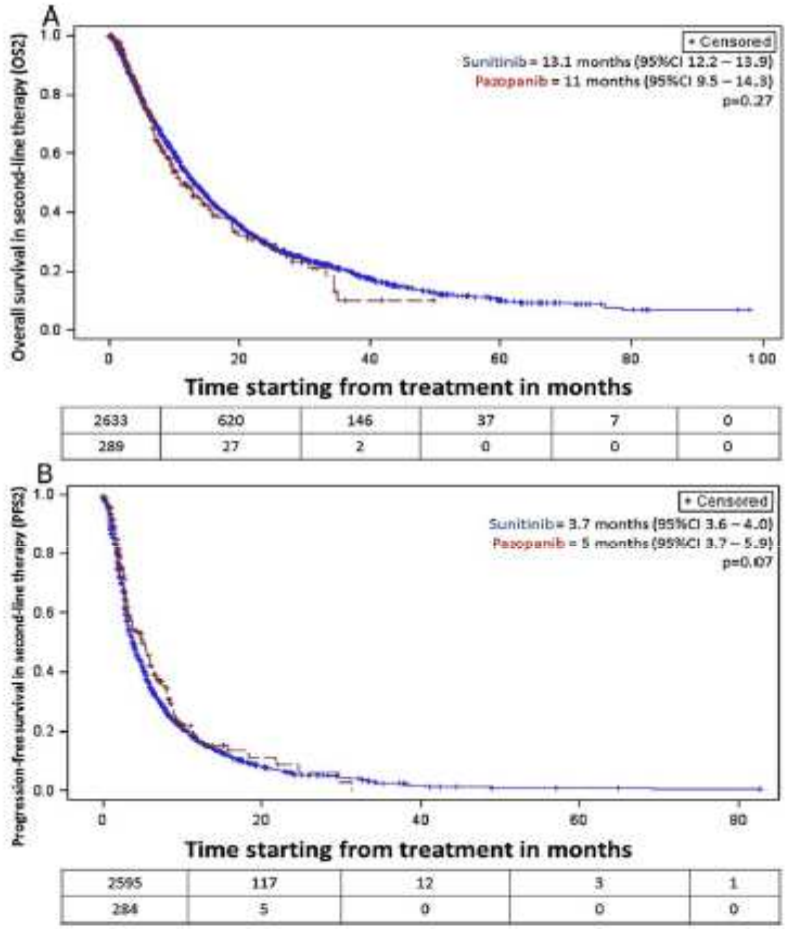


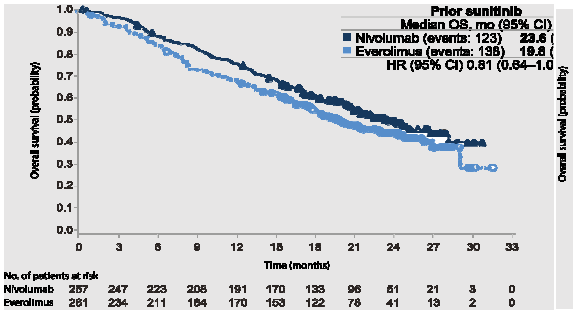
Fig. 3. (A) Overall survival in second-line therapy after either sunitinib (SU) or pazopanib (PZ). (B) Progression-free survival in second-line therapy after either SU or PZ.

VEGF receptor inhibitors may improve overall survival and objective response rate when used before nivolumab

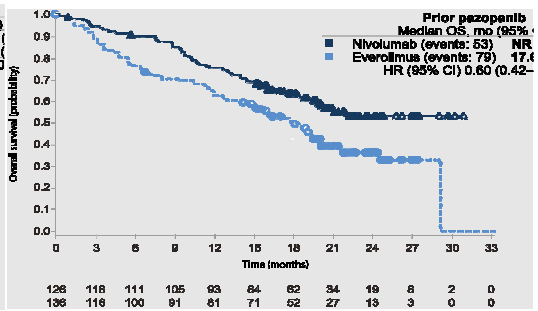
Nivolumab is effective in aRCC patients previously treated with antiangiogenic agents such as sunitinib and pazopanib[1]

OS with nivolumab was 23.6 months (95% CI, 20.4–28.1) with prior sunitinib and NE (95% CI, 19.7–NE) with prior pazopanib[1]

OS with prior sunitinib[1]



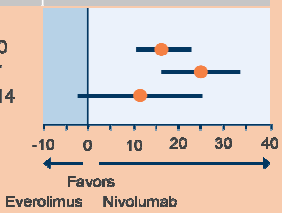
OS with prior pazopanib[1]



Objective response rate Forest plot by prior therapy[1]

Nivolumab objective response rate was 28% following pazopanib (95% CI: 20–37) and 23% following sunitinib (95% CI: 18–28)

	Nivolumab		Everolimus		ORR difference
Subgroup	ORR, %	95% CI	ORR, %	95% CI	(95% CI)
Prior therapy					
Sunitinib	23	18–28	6	4–10	
Pazopanib	28	20–37	3	1–7	
IL-2	14	5–29	3	0.1–14	



aRCC, advanced renal cell carcinoma; CI, confidence interval; HR, hazard ratio; IL, interleukin; NE, not evaluable; NR, not reached; ORR, objective response rate; OS, overall survival; VEGF, vascular endothelial growth factor

1. Escudier B, et al. Eur Urol 2017;72(6):962–971.

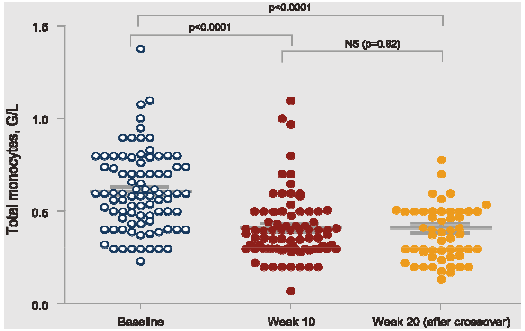
1L pazopanib may improve 2L immunotherapy response in a/mRCC

- Pazopanib has a range of immunomodulatory effects:

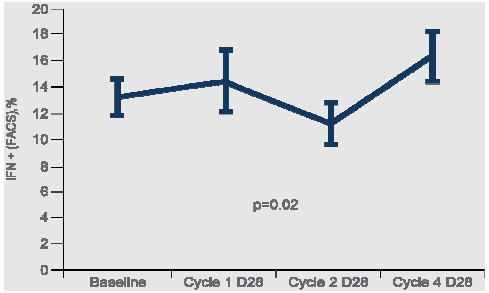
Altered amounts and types of cells within tumor environment[1,2]	Prevent immunosuppression and increase T cell toxicity
Increase in PD-L1 expression in the immune component[3]	May facilitate 2L therapeutic targeting by presenting more binding sites
In patients with aRCC, there is a trend toward better outcomes with 2L nivolumab when pazopanib is used first, in comparison with using sunitinib first[4]	May condition a tumor environment for better 2L responses

Enhanced response of 2L immunotherapy in a/mRCC may be due to an immuno-conditioning class effect of VEGF receptor inhibitors

Reduction in immunosuppressive cell types after pazopanib or sunitinib treatment[1]



Restoration of anti-tumor immunity after pazopanib treatment[2]



1L, first line; 2L, second line; aRCC, advanced renal cell carcinoma; D, day; FACS, fluorescence-activated cell sorting; IFN, interferon; mRCC, metastatic renal cell carcinoma; NS, not significant; PD-L1, programmed cell death ligand 1; VEGF, vascular endothelial growth factor

1. Oudard S *et al.* Presented at: 2015 ECCO-ESMO meeting; 25-29 Sept 2015; Vienna, Austria. Abstract 433. 2. Khurhana KK *et al.* Poster presented at the 2013 ASCO meeting; May 31-June 4, 2013; Chicago, IL. Abstract 455. 3. Powles T, et al. JAMA Oncol 2016;2(10):1303–1309.4. Escudier B, et al. Eur Urol 2017;72(6):962–971.

1st line treatment of metastatic renal cell carcinoma/Poland/poor group

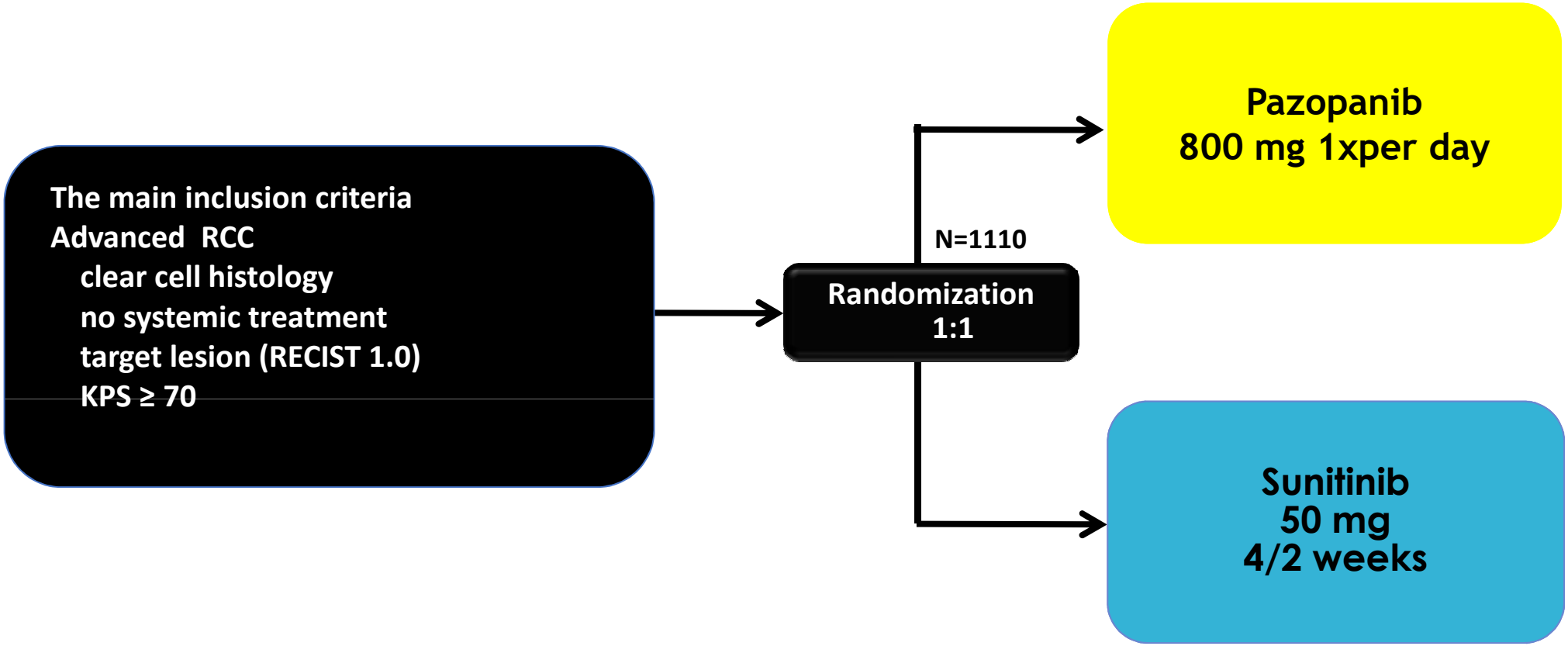
Overall survival (months):

- Interferon 7,3
- Temsirolimus 10,9 **(HR for death, 0.73; 95%, [CI], 0.58 to 0.92; *p=0.008*)**
- Inteferon + Temsirolimus 8,4

Hudes G, Carducci M, Tomczak P i wsp. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med (2007); 356(22): 2271-2281.

Step 3. Factors that are related to the patient.

COMPARZ study

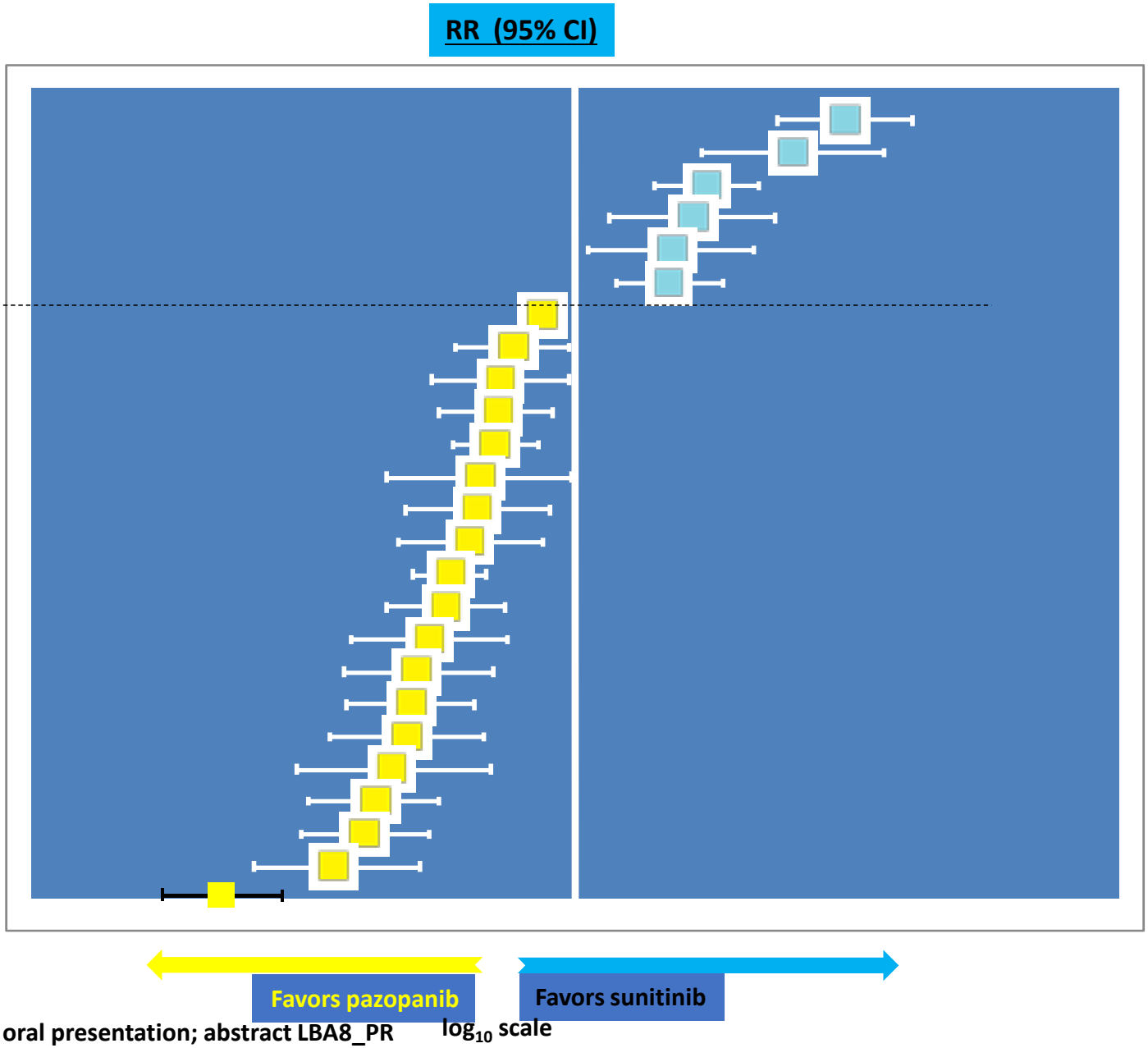


1. Motzer R, *et al.* ESMO 2012 oral presentation; abstract LBA8_PR.

The Relative Risk of Incidence of Adverse Events

Side effects*

- Hair color change
- Weight loss
- Increase ALT
- Alopecia
- Pain in the epigastrium
- Wzrost stężenia AST
- Fatigue
- Rash
- Pain in the limbs
- Constipation
- Disorder of taste
- Increase LDH
- Increase in creatinine
- Peripheral edema
- Hand-foot syndrome
- Dyspepsia
- Fever
- Leucopenia
- Hypothyroidism
- Epistaxis
- Increase TSH
- Inflammation of mucous membranes
- Neutropenia
- Anemia
- Thrombocytopenia



1. Motzer R, *et al.* ESMO 2012 oral presentation; abstract LBA8_PR

Increased activity of liver enzymes (≤35%)[1] laboratory values

Increased activity of liver enzymes,* %	Pazopanib (n=554)		Sunitinib (n=548)	
	All grades	Grade 3/4	All grades	Grade 3/4
ALT	60	15/2	43	4/<1
AST	61	11/1	60	3/0
Bilirubin	36	3/<1	27	2/<1
Albumin	33	<1/0	42	2/0
Creatinine	32	<1/0	46	<1<1
Hyperglycaemia	54	5/0	57	4/<1

Motzer R, *et al.* ESMO 2012 oral presentation; abstract LBA8_PR.

Haematologic toxicity (≥35%)[1]

Haematologic toxicity, * %	Pazopanib (n=554)		Sunitinib (n=548)	
	All grades	Grade 3/4	All grades	Grade 3/4
Anemia	31	1/<1	60	6/1
Neutropenia	37	4/<1	68	19/1
Thrombocytopenia	41	3/<1	78	18/4
Lymphocytopenia	38	5/0	55	14/<1
Leucopenia	43	1/0	78	6/0

Motzer R, *et al.* ESMO 2012 oral presentation; abstract LBA8_PR.

Step 4. Potential biomarkers, related to cancer.

Prognostic versus predictive biomarkers

Prognostic Biomarkers

Biomarkers classify patients into groups with good, intermediate or poor prognosis, regardless of the type of therapy

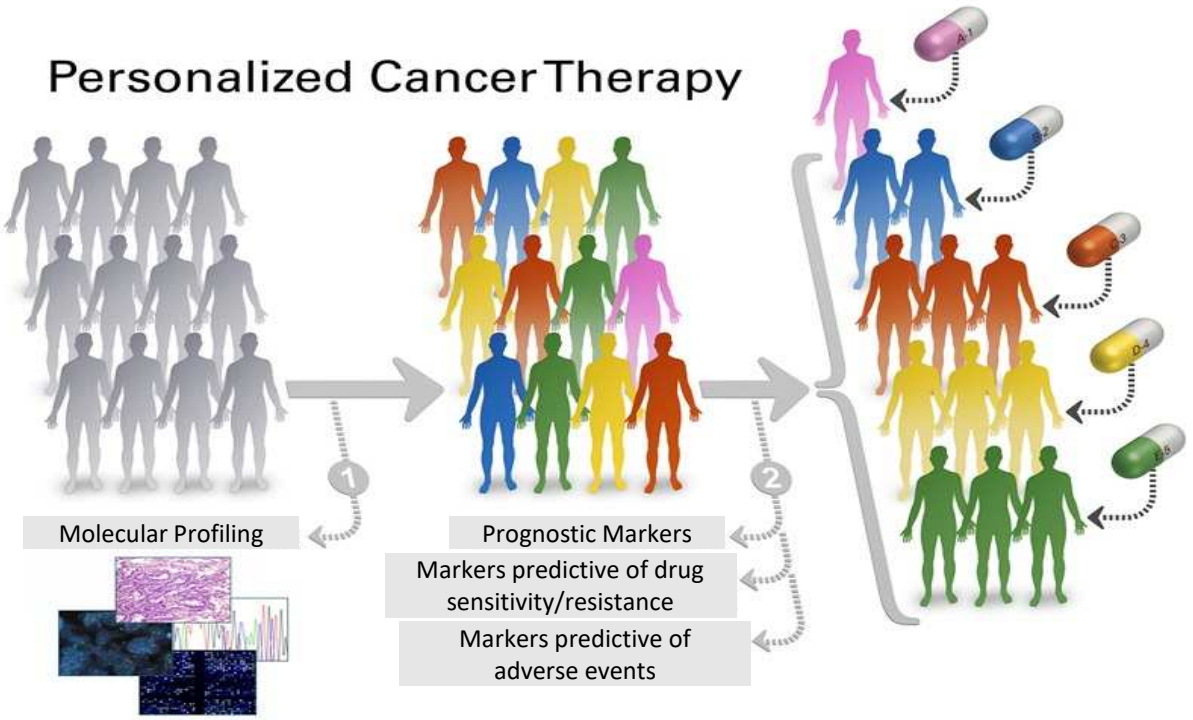
Predictive Biomarkers

Biomarkers identify patients who can benefit from individual treatment regimens

Potential biomarkers under evaluation

Candidate Biomarker	Prospective Studies in RCC
PD-L1 expression	• **Nivolumab vs everolimus** • **Atezolizumab** • **Pazopanib vs sunitinib**
***VEGFR-1* polymorphisms**	• **Bevacizumab** • **Axitinib vs sunitinib**
***IL-8* polymorphisms**	• **Pazopanib** • **Sunitinib**
***PBRM1, SETD2, BAP1,* or *KDM5C* mutation in chromatin-modifying genes**	• **Everolimus vs sunitinib**
High circulating IL-18 levels	• **Everolimus vs sunitinib**

The development of genomics and advanced multiplatform technology can lead to the personalization of therapy and the new classification of kidney cancers



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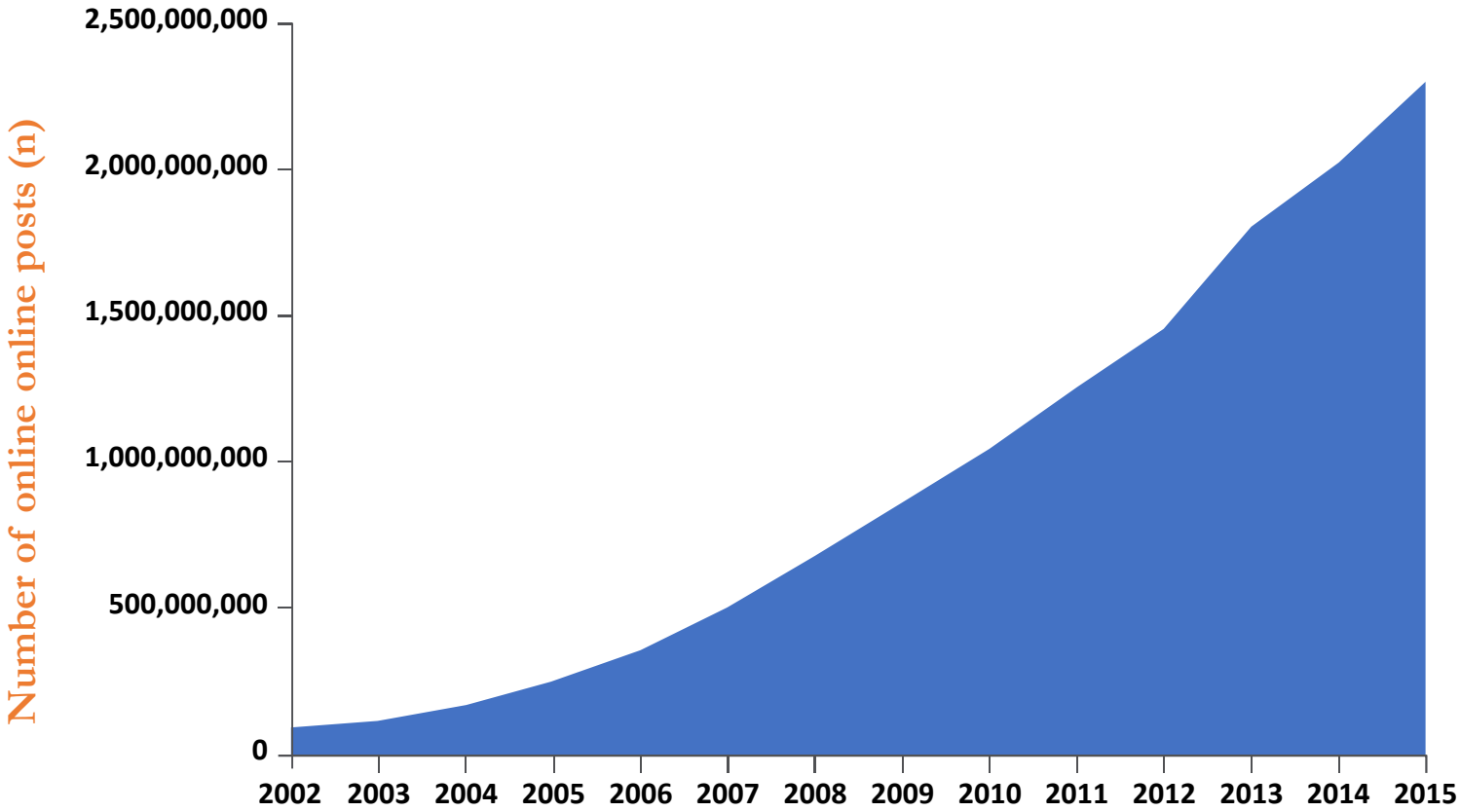
Step 5. Patient’s choice.

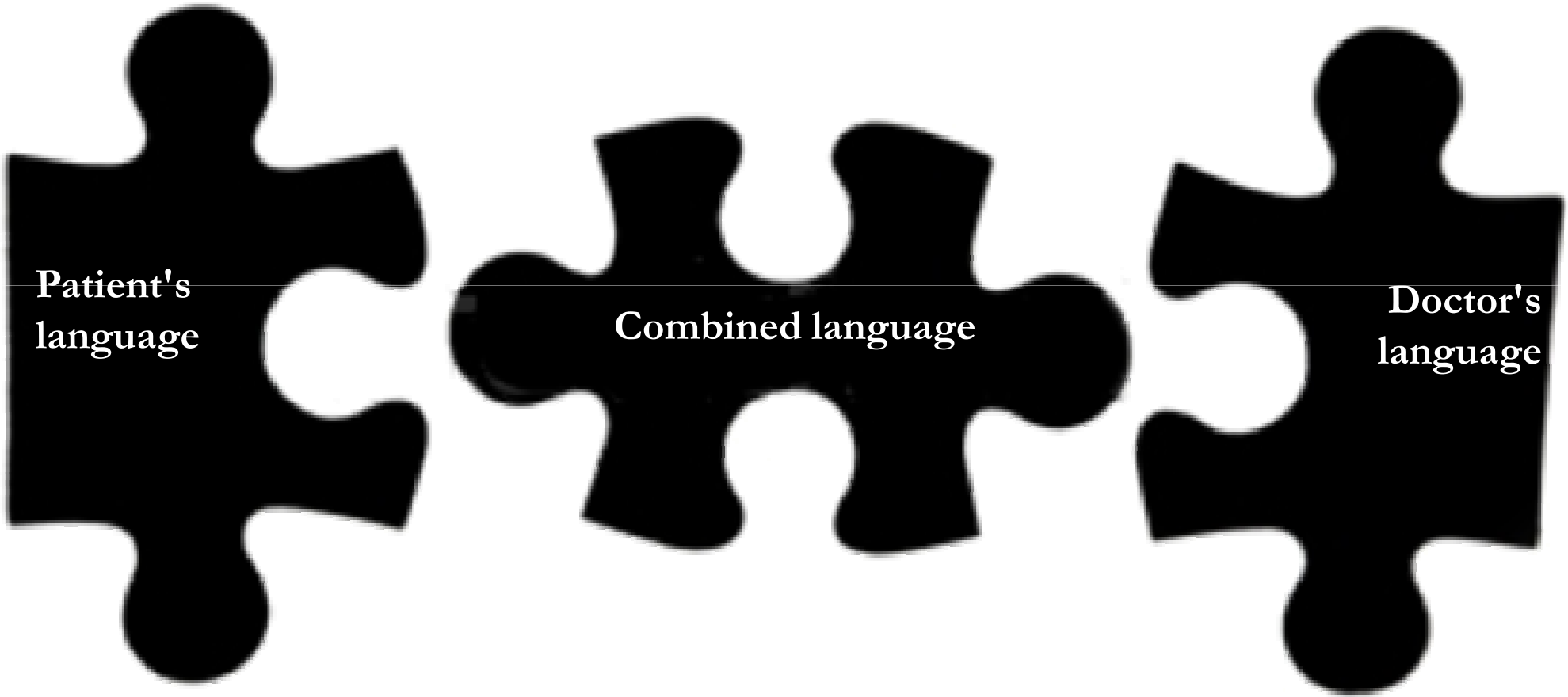
The increase in the number of patients and their families participating in online "disease" communities



Data collected from open-source communities; not collected from closed-source communities, except in instances involving partnerships.

Source: Treato. December 2015.

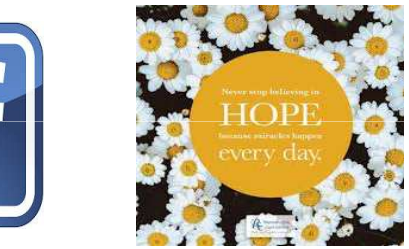
Understanding and adapting the "language" to the patient

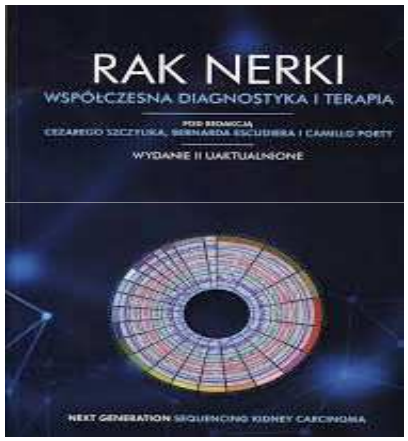


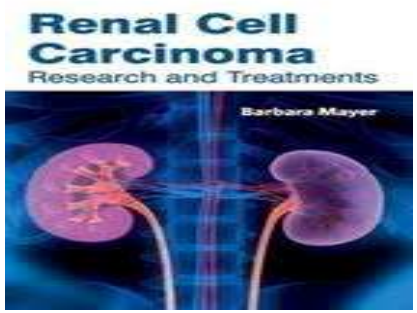
When the patients have not received enough information from the doctor…….

- **Patients are looking for information online ……**

Google







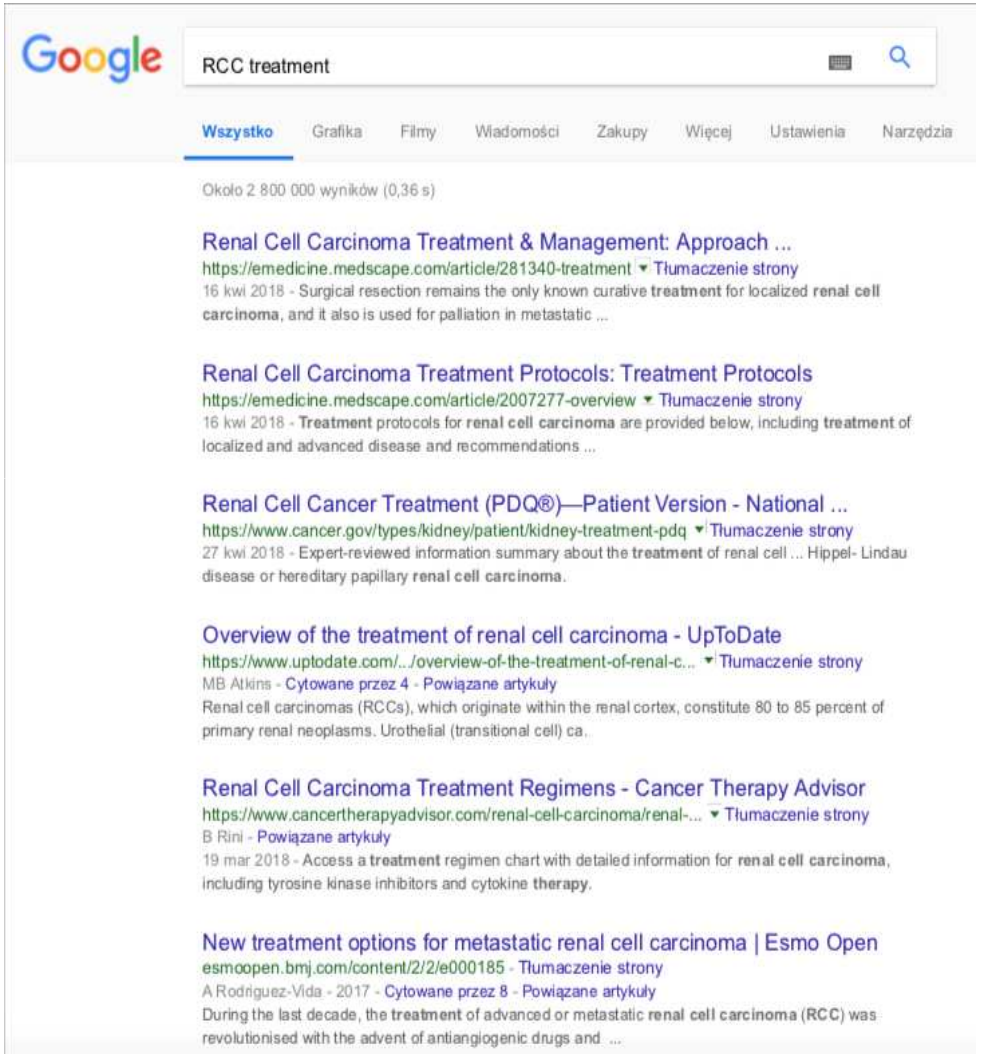
my day

Stowarzyszenie na rzecz Wspierania Dolnośląskiej Nefrologii, Dializoterapii i Transplantologii
PRO RENIS

Fallowfield DL ESMO 2016
Stec R 2018

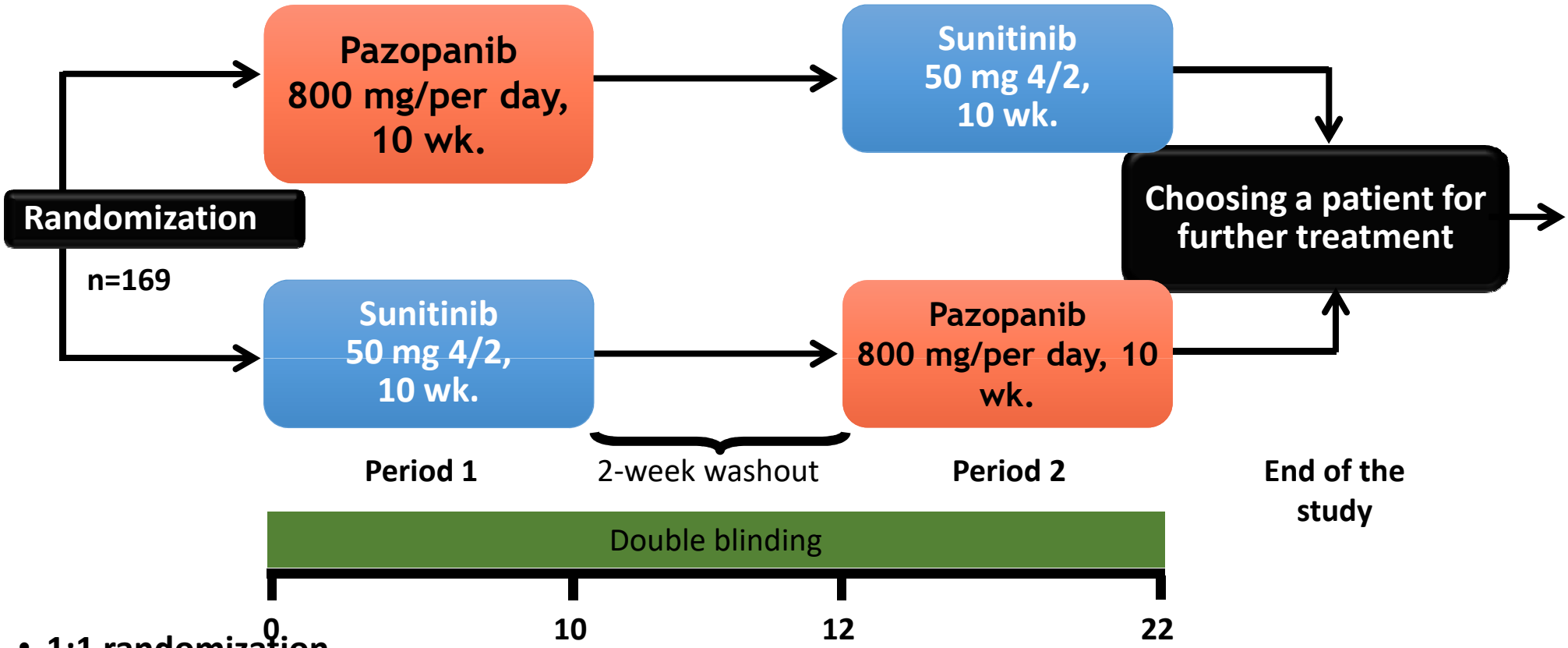
Google search

- **Information changes every day**
- **A lot of information is helpful**
- **Some information is harmless**
- **Some information is dangerous or false**



Stec R 2018

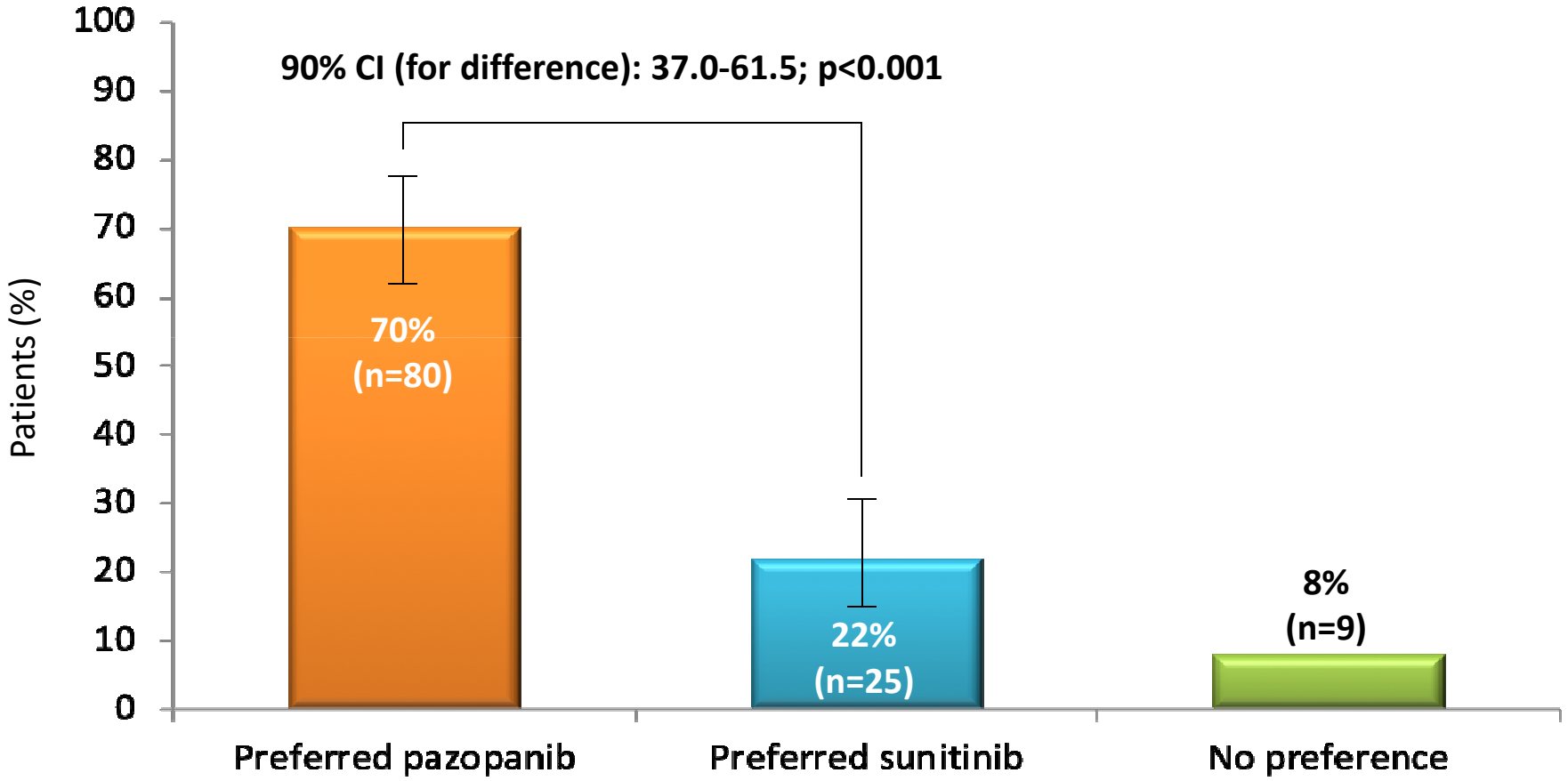
PISCES study



- 1:1 randomization
- Both drugs were encapsulated
- Patients treated with sunitinib received placebo in 2 weeks without treatment

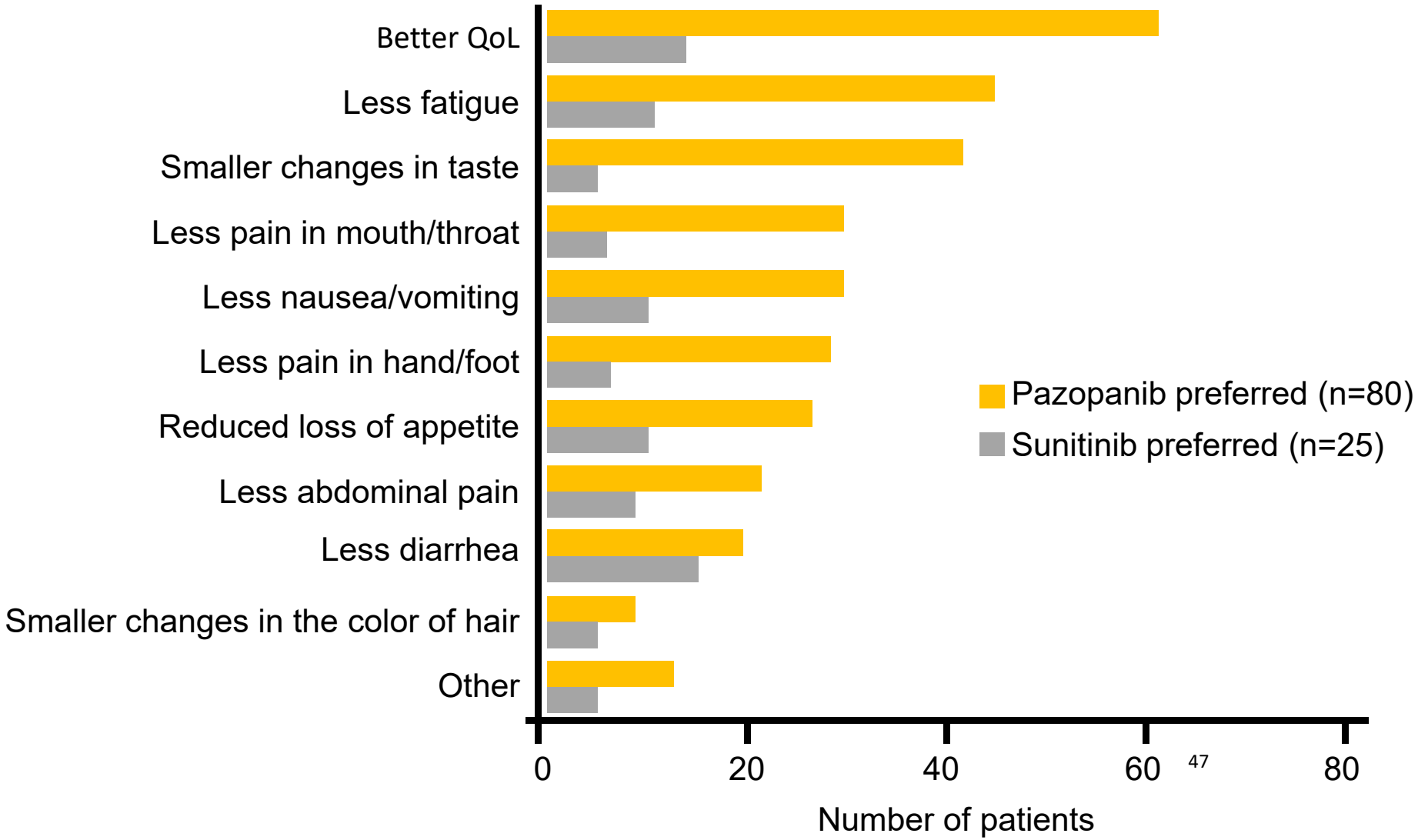
1. ClinicalTrials.gov. NCT01064310.

Primary Endpoints: Patient's preferences in the PISCES Study



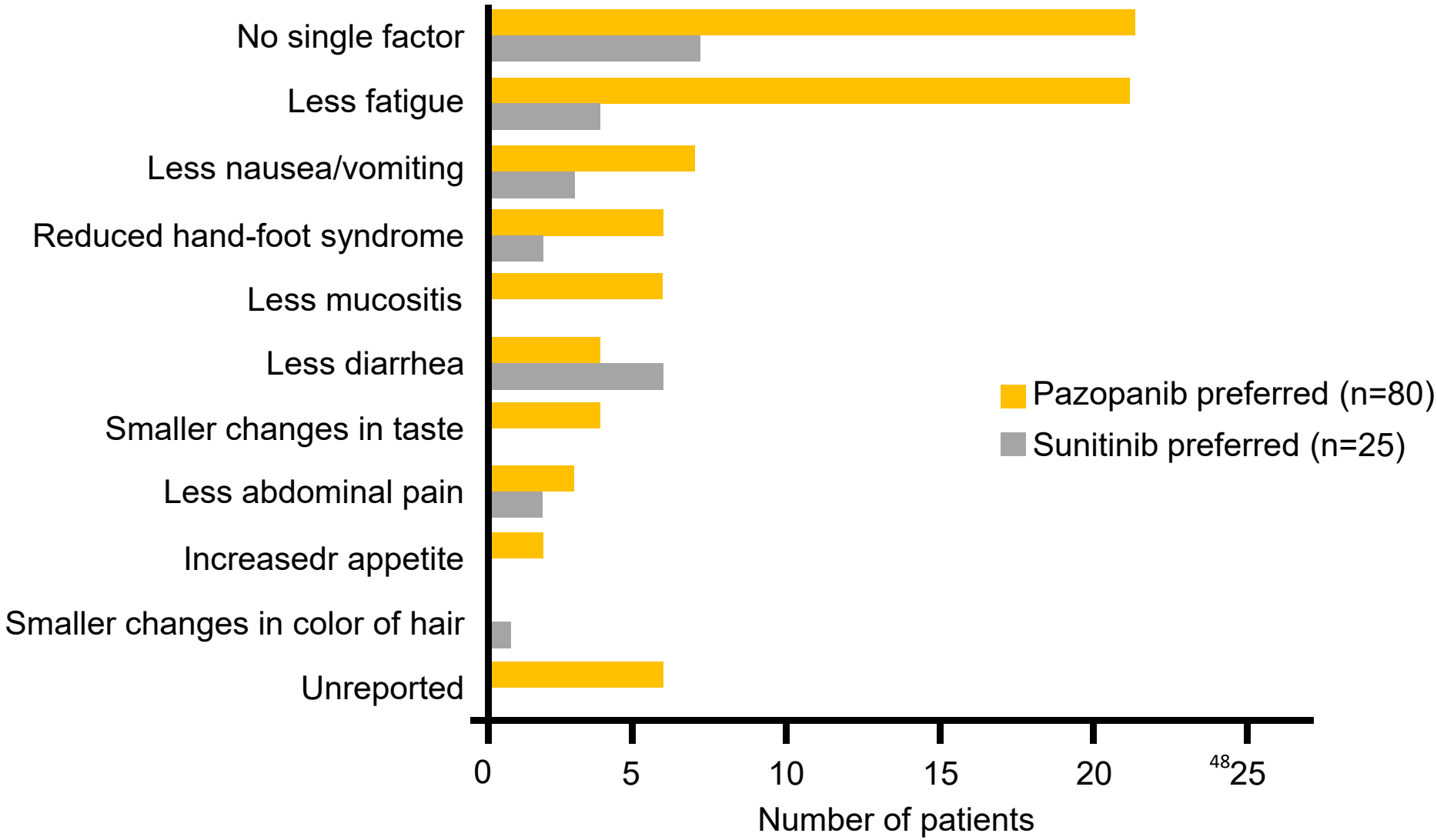
1. Escudier B, *et al*. ASCO 2012 oral presentation; abstract 4502.

Factors associated with the choice of treatment:



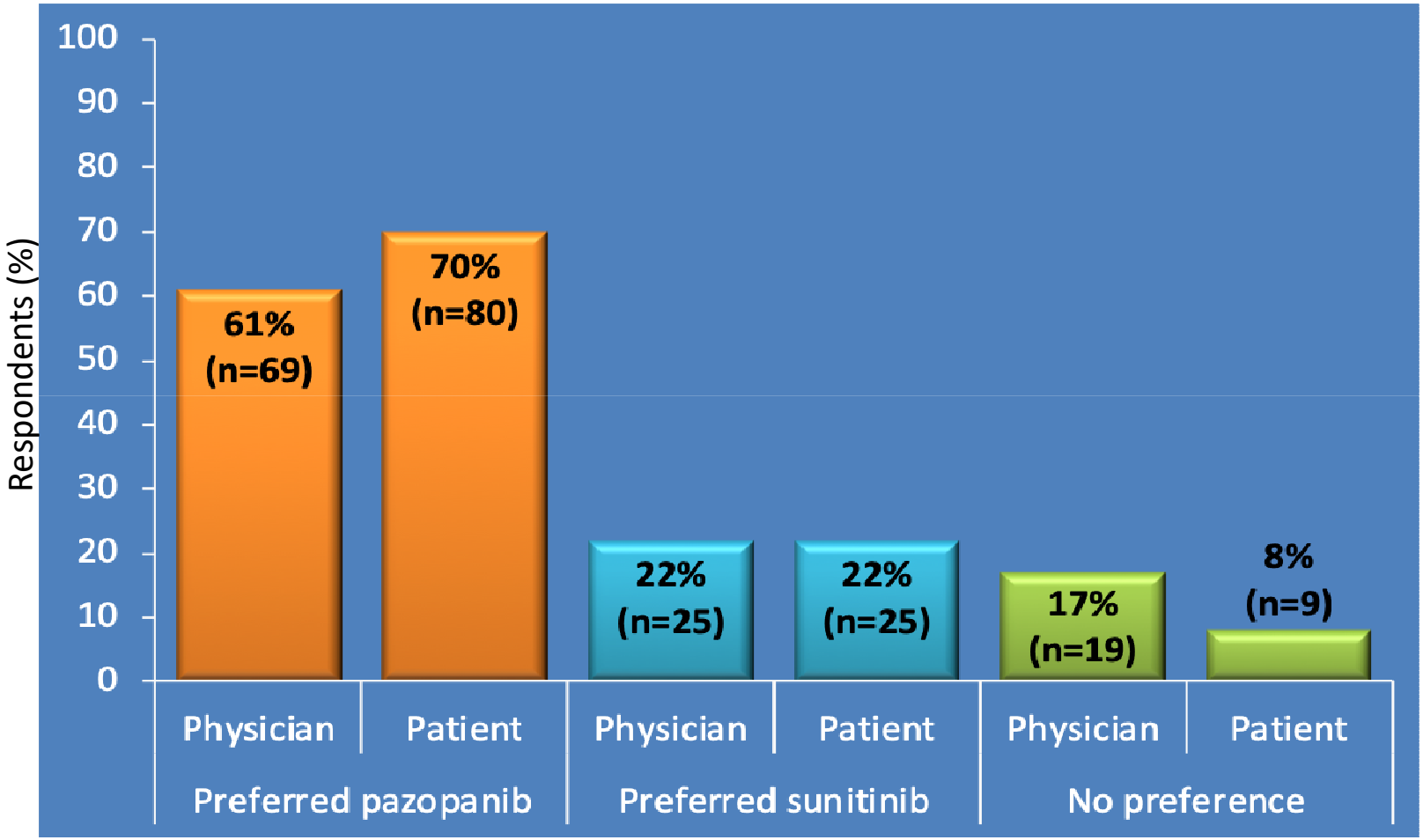
1. Escudier *et al. J Clin Oncol* 2014;32:1412–8.

The most important single factor affecting patient selection



1. Cella *et al*. ESMO 2012;Abstract 792PD (Poster).

Doctor's preferences regarding drugs used in the study (primary analysis)[1]



Doctor's preferences are extremely important because they also include side effects that are not noticed by patients

Escudier B, *et al.* ASCO 2012 oral presentation; abstract 4502.

Take home massage

- **Step 1.Staging the disease.**
- **Step 2. The prognostic group of patients.**
- **Step 3. Factors that are related to the patient.**
- **Step 4. Potential biomarkers that are related to cancer.**
- **Step 5. Patient’s choice.**

Are we ready for a new standard?

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/Toxicity	MCBS Score[b]
Nivolumab, a PD-1 checkpoint inhibitor	Advanced clear cell renal cell carcinoma previously treated with one or two regimens of anti-angiogenic therapy	Study of nivolumab vs. everolimus in pre-treated advanced or metastatic clear-cell renal cell carcinoma (CheckMate 025) [50] Phase III NCT01668784	Everolimus Median OS: 19.6 months	OS gain: 5.4 months	OS HR: 0.73 (0.57–0.93)	Improved toxicity profile and QoL	5 (Form 2a)
Cabozantinib	Advanced renal cell carcinoma in adults following prior vascular endothelial growth factor receptor tyrosine kinase inhibitors	A study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma (METEOR) [52] Phase III NCT01865747	Everolimus Median OS: 16.5 months	OS gain: 4.9 months	OS HR: 0.66 (0.53–0.83)	—	3 (Form 2a)
Lenvatinib in combination with everolimus	Advanced or metastatic renal cell carcinoma following one prior vascular endothelial growth factor-targeted therapy	Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial [53] Phase II NCT01136733	Everolimus Median OS: 15.4 months	OS gain: 10.1 months	OS HR: 0.51 (0.30–0.88)	—	4 (Form 2a; secondary endpoint of OS in a small phase II randomised study)
Nivolumab in combination with ipilimumab	First-line therapy for intermediate- and poor-risk advanced metastatic renal cell carcinoma	Nivolumab plus ipilimumab versus sunitinib in advanced renal cell carcinoma (CheckMate 214) [28, 69] Phase III NCT02231749	Sunitinib Median OS: 26.0 months	OS gain: 7.3 months[c]	OS HR: 0.63 (0.44–0.89)	QoL benefit reported in exploratory evaluation[d]	3 (Form 2a)
Tivozanib	Recurrent or metastatic renal cell carcinoma with clear cell component, and prior nephrectomy	Tivozanib versus sorafenib in patients with advanced renal cell carcinoma [45] Phase III NCT01030783	Sorafenib Median PFS: 9.1 months	PFS gain: 2.8 months	PFS HR: 0.80 (0.64–0.99)	OS NS No QoL benefit	1 (Form 2b)

Escudier, et al. Ann Oncol. 2019, doi.org/10.1093/annonc/mdz056

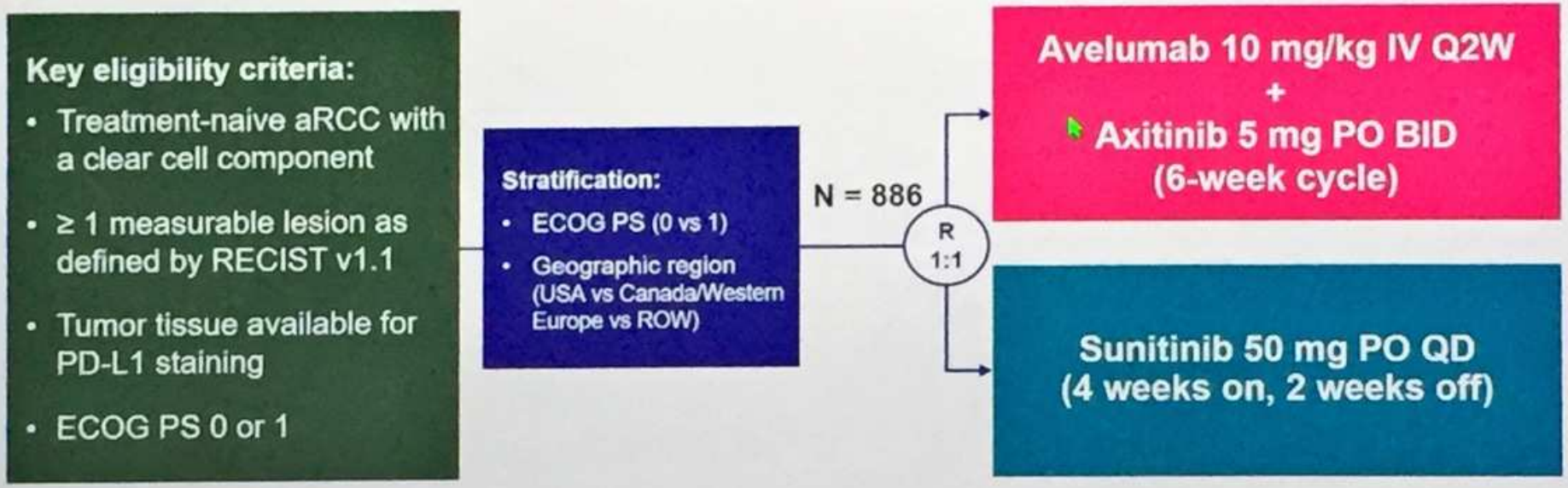
Guidelines for treatment of mRCC - ESMO 2019

Setting	Risk group	Standard	Option
First line	Good risk	Sunitinib [I,A] Bevacizumab + IFN-α [I,A] Pazopanib [I,A] Tivozanib [IIA}	High-dose IL2 [III,B] Bevacizumab + low-dose IFN-α [III,B]
	Intermediate/Poor risk	Nivolumab + Ipilimumab [I,A]	Cabozantinib [II,A]/Cabozantinib [II,C] Sunitinib [I,B]/Sunitinib [II,C] Pazopanib [I,B]/Pazopanib [II,C] Tivozanib [II,B]/Temsirolimus [I,C] Bevacizumab + IFN-α [II,C]/----------
Second line	Post TKI	Nivolumab [I,A, MCBS 5] Cabozantinib [I,A, MCBS 3] Tivozanib [II,C, MCBS 1]	Axitinib [II,B] Everolimus [II,B] Levantinib + Everolimus [II,B, MCBS 4]
	Post Nivolumab + Ipilimumab	----------	Any TKI [IV,C] Levantinib + Everolimus [IV,C, MCBS 4]
Third line	First line - TKI Second line - Nivolumab	Cabozantynib [IV,B]	Axitibib [II,B] Everolimus [V,C]
	First line - TKI Second line - Cabozantinib	Nivolumab [II,B, MCBS 5]	Axitibib [V,C] Everolimus [V,C]
	First line - TKI Second line - TKI	Cabozantinib [I,A] Nivolumab [I,A, MCBS 5]	Everolimus [V,C]
	First line - Nivolumab + Ipilmumab Second line - TKI	Nivolumab [V,A]	Another TKI [V, C] Everolimus [V,C]

Escudier, et al. Ann Oncol. 2019, doi.org/10.1093/annonc/mdz056

And……

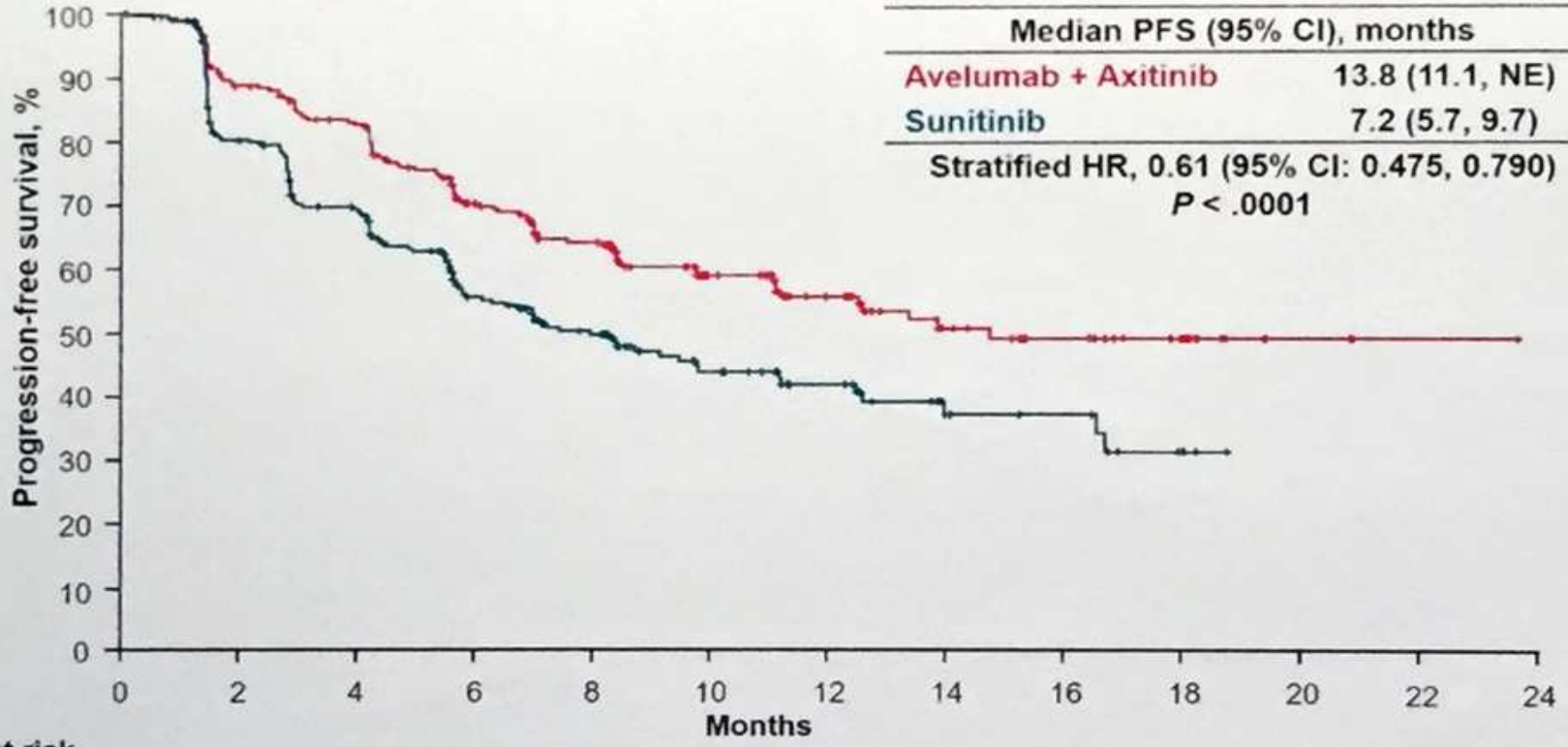
JAVELIN RENAL 101: STUDY DESIGN



BID, twice per day; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **IV**, intravenous; **PO**, orally; **Q2W**, every 2 weeks; **QD**, once per day; **ROW**, rest of the world.

Primary endpoint

PRIMARY ENDPOINT #1 MET: PFS PER IRC IN THE PD-L1+ GROUP



Median PFS (95% CI), months	
Avelumab + Axitinib	13.8 (11.1, NE)
Sunitinib	7.2 (5.7, 9.7)

Stratified HR, 0.61 (95% CI: 0.475, 0.790)
P < .0001

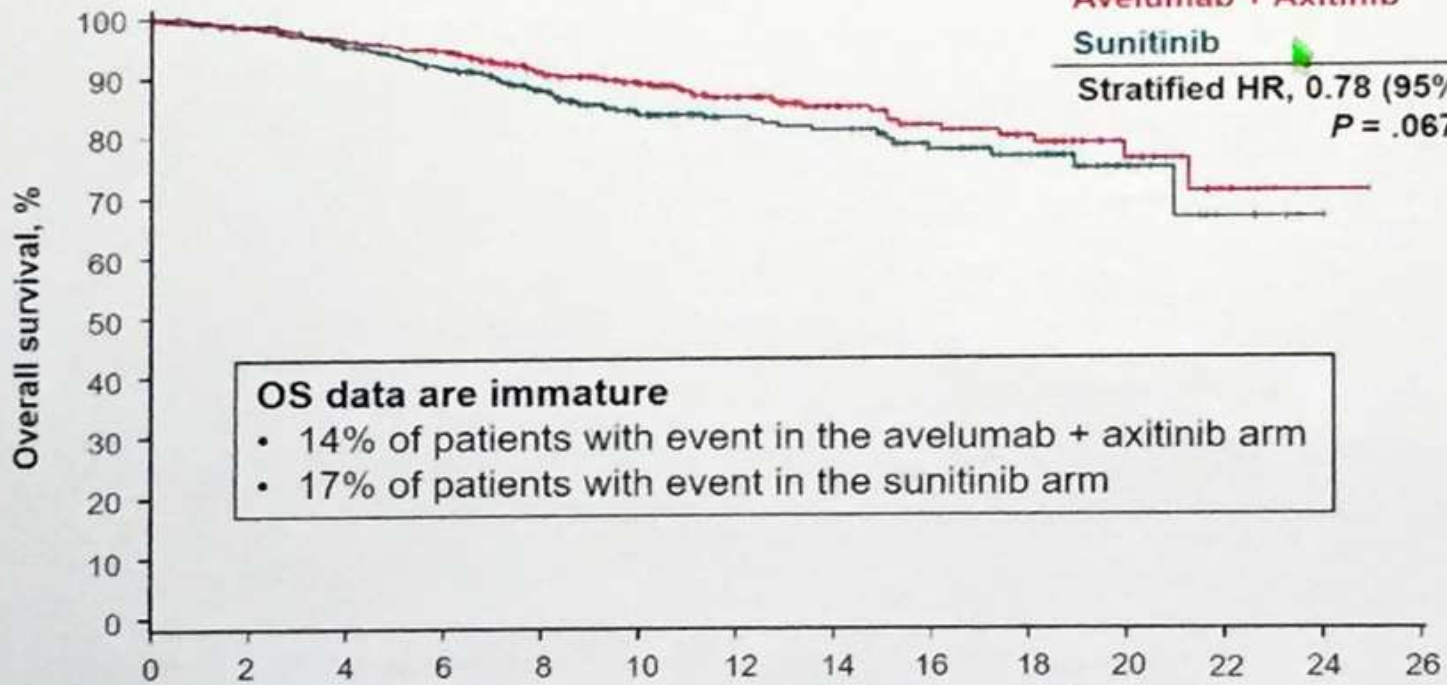
Number at risk

Avel + Axit:	270	227	205	154	120	76	53	32	23	13	3	1	0
Sunitinib:	290	210	174	119	85	49	35	16	13	5	0		

Minimum follow-up, 6 months. Median follow-up, 9.9 months (avelumab + axitinib) and 8.4 months (sunitinib).
The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* = .001).

NE, not estimable.

OS in the overall population



Number at risk

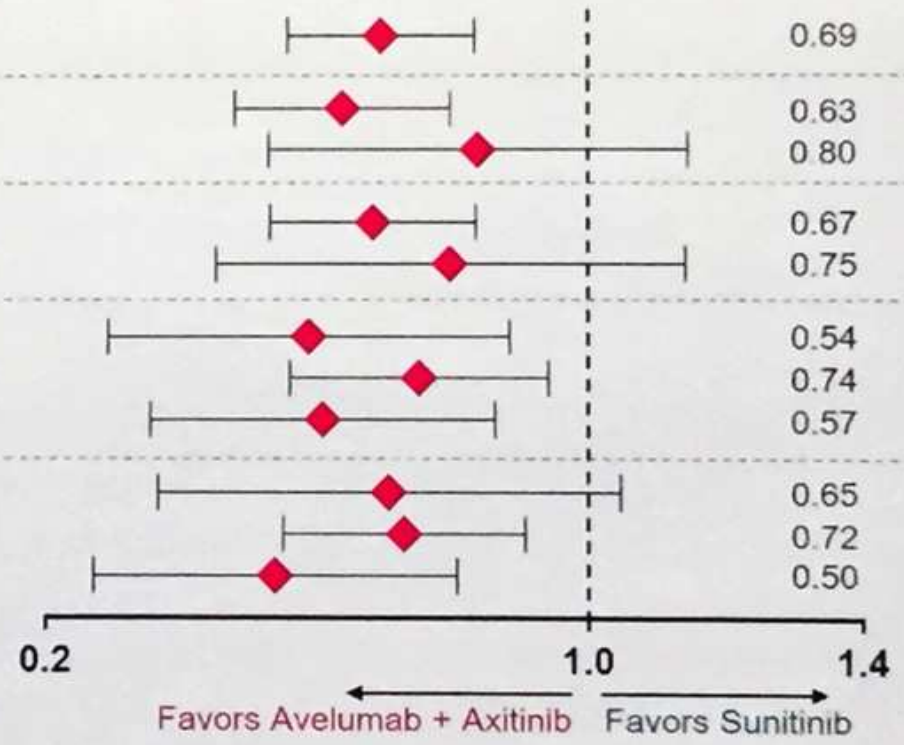
Avel + Axit:	442	426	412	396	319	252	187	121	93	70	27	8	1	0
Sunitinib:	444	426	401	373	295	224	175	113	84	59	17	5	1	0

Median follow-up, 12.0 months (avelumab + axitinib) and 11.5 months (sunitinib)

PFS PER IRC IN KEY SUBGROUPS

Subgroup analysis

Subgroup		Events/patient: Avelumab + Axitinib	Events/patient: Sunitinib	HR
Overall population		180/442	216/444	0.69
PD-L1 group*	Positive	108/270	145/290	0.63
	Negative	54/132	58/120	0.80
Prior nephrectomy	Yes	143/352	172/355	0.67
	No	37/90	44/89	0.75
IMDC risk	Favorable	25/94	36/96	0.54
	Intermediate	112/271	129/276	0.74
	Poor	41/72	50/71	0.57
MSKCC risk	Favorable	29/96	36/100	0.65
	Intermediate	118/283	142/293	0.72
	Poor	29/51	34/45	0.50



* Among patients not evaluable for PD-L1 expression, PFS events occurred in 18/40 patients (avelumab + axitinib) vs 13/34 patients (sunitinib); HR, 0.83; 95% CI: 0.403, 1.699

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 2, 2018 VOL. 379 NO. 5

Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma

A. Méjean, A. Ravaud, S. Thezenas, S. Colas, J.-B. Beauval, K. Bensalah, L. Geoffrois, A. Thiery-Vuillemin, L. Cormier, H. Lang, L. Guy, G. Gravis, F. Rolland, C. Linassier, E. Lechevallier, C. Beisland, M. Aitchison, S. Oudard, J.-J. Patard, C. Theodore, C. Chevreau, B. Laguerre, J. Hubert, M. Gross-Goupil, J.-C. Bernhard, L. Albiges, M.-O. Timsit, T. Lebret, and B. Escudier

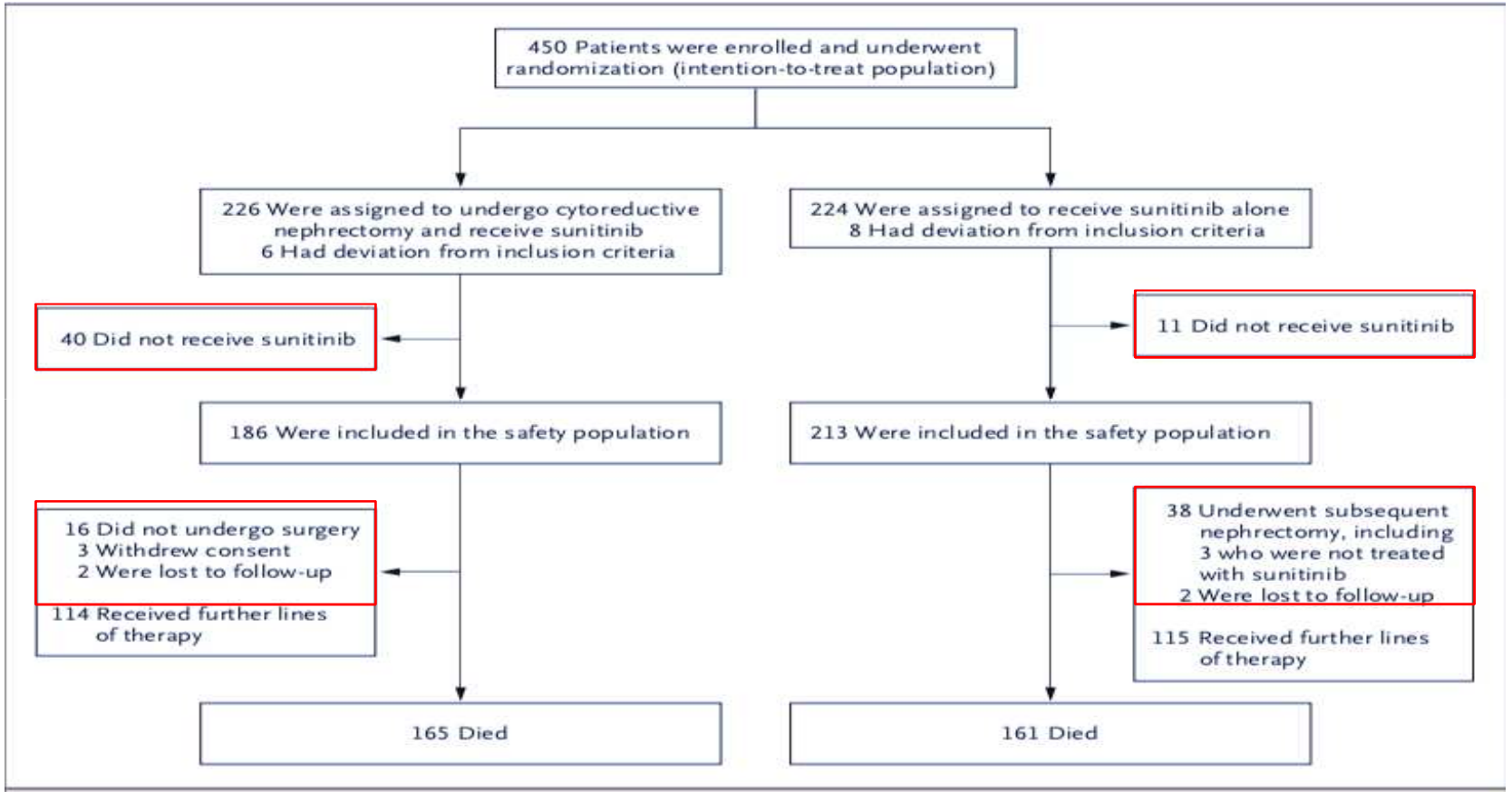
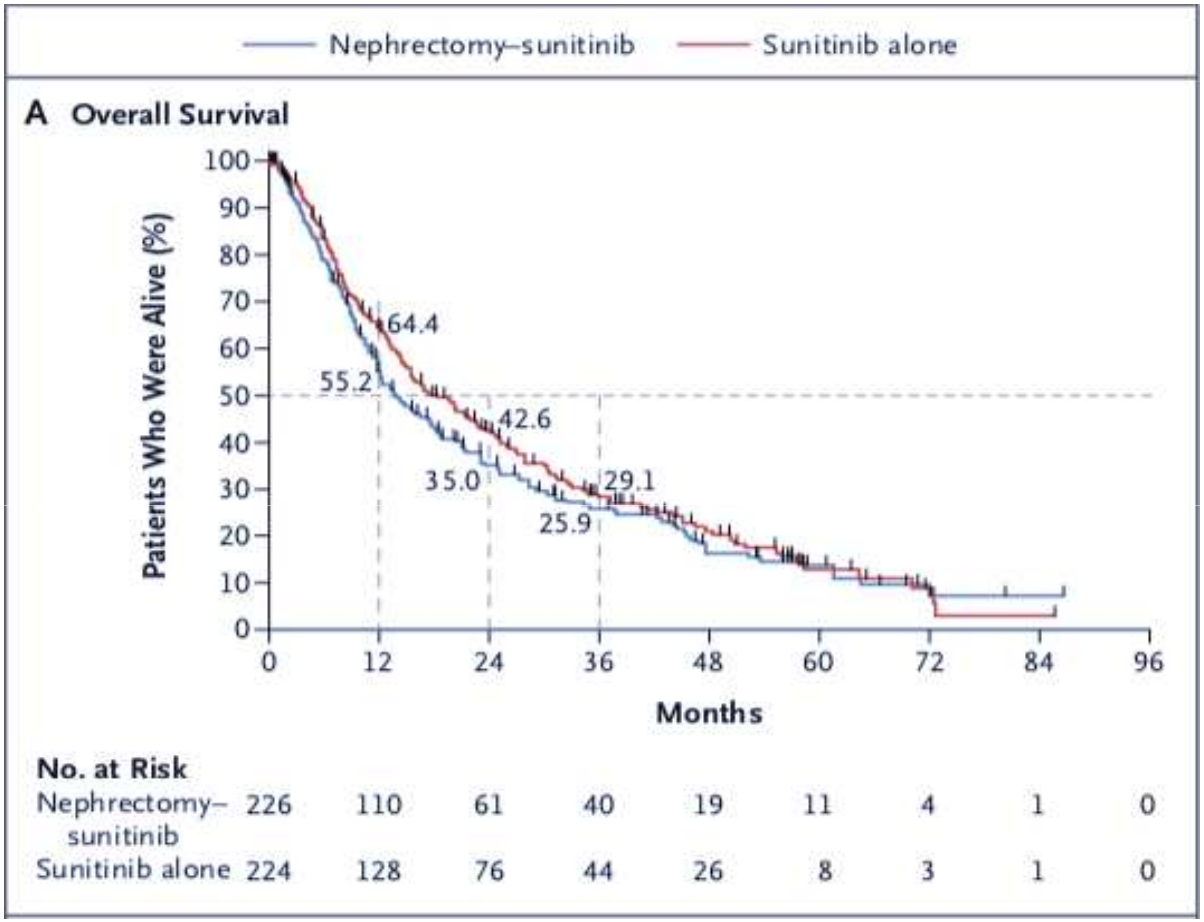
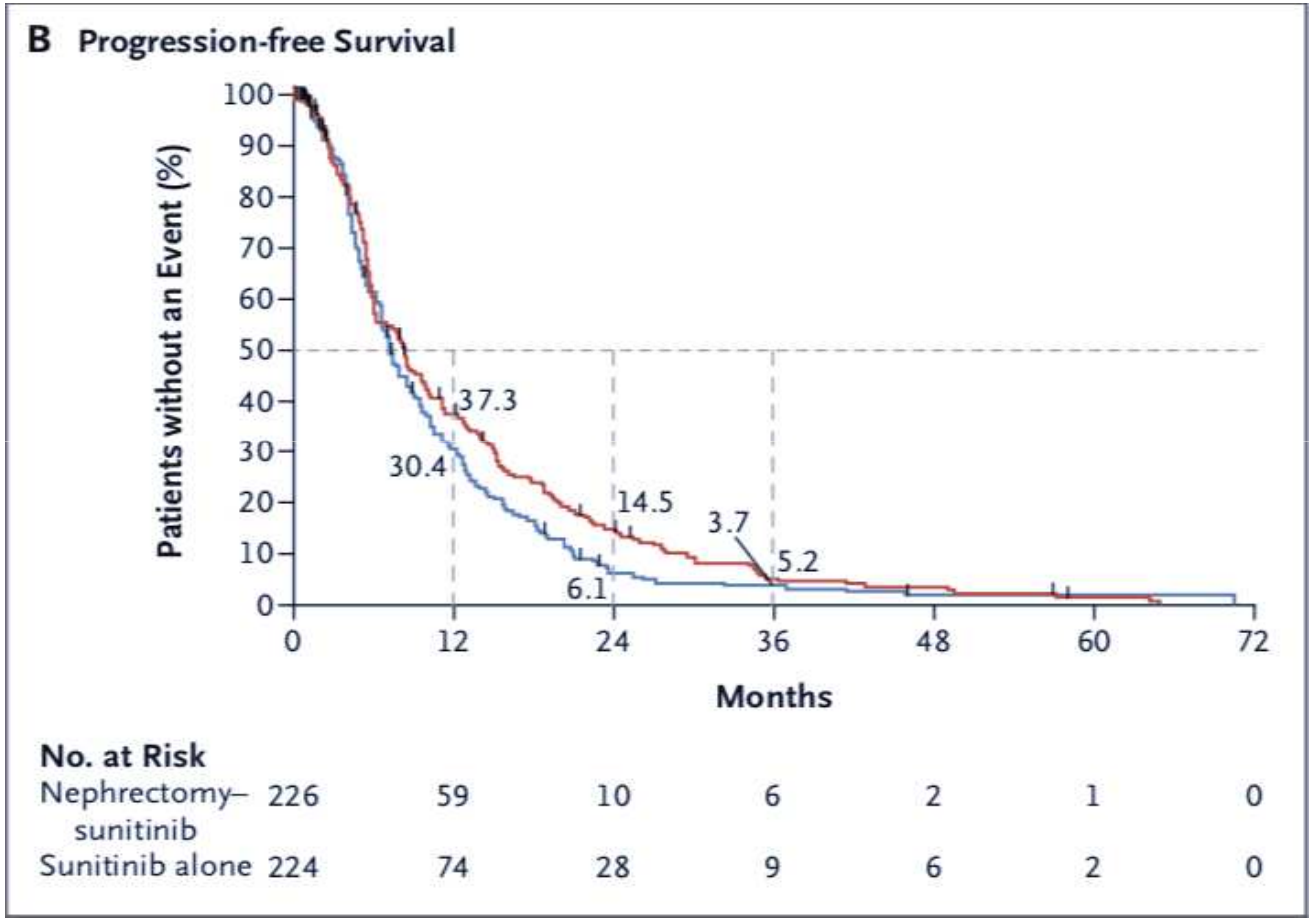


Figure 1. Randomization, Treatment, and Follow-up of the Patients.


Nephrectomy–sunitinib
Sunitinib alone
A Overall Survival
Patients Who Were Alive (%)
100
90
80
70
60
50
40
30
20
10
0
64.4
55.2
42.6
35.0
29.1
25.9
0
12
24
36
48
60
72
84
96
Months
No. at Risk
Nephrectomy–sunitinib 226 110 61 40 19 11 4 1 0
Sunitinib alone 224 128 76 44 26 8 3 1 0


B Progression-free Survival
Patients without an Event (%)
100
90
80
70
60
50
40
30
20
10
0
37.3
30.4
14.5
3.7
5.2
6.1
0
12
24
36
48
60
72
Months
No. at Risk
Nephrectomy–sunitinib 226 59 10 6 2 1 0
Sunitinib alone 224 74 28 9 6 2 0

RESULTS

A total of 450 patients were enrolled from September 2009 to September 2017. At this planned interim analysis, the median follow-up was 50.9 months, with 326 deaths observed. The results in the sunitinib-alone group were noninferior to those in the nephrectomy–sunitinib group with regard to overall survival (stratified hazard ratio for death, 0.89; 95% confidence interval, 0.71 to 1.10; upper boundary of the 95% confidence interval for noninferiority, ≤1.20). The median overall survival was 18.4 months in the sunitinib-alone group and 13.9 months in the nephrectomy–sunitinib group. No significant differences in response rate or progression-free survival were observed. Adverse events were as anticipated in each group.

CONCLUSIONS

Sunitinib alone was not inferior to nephrectomy followed by sunitinib in patients with metastatic renal-cell carcinoma who were classified as having intermediate-risk or poor-risk disease. (Funded by Assistance Publique–Hôpitaux de Paris and others; CARMENA ClinicalTrials.gov number, NCT00930033.)

Conclusion

Sunitinib alone was not inferior to nephrectomy followed by sunitinib in patients with metastatic renal-cell carcinoma who were in the MSKCC intermediate - risk or poor-risk groups.

But …….. due to some doubts, we should abstain from the final announcement of the standard!

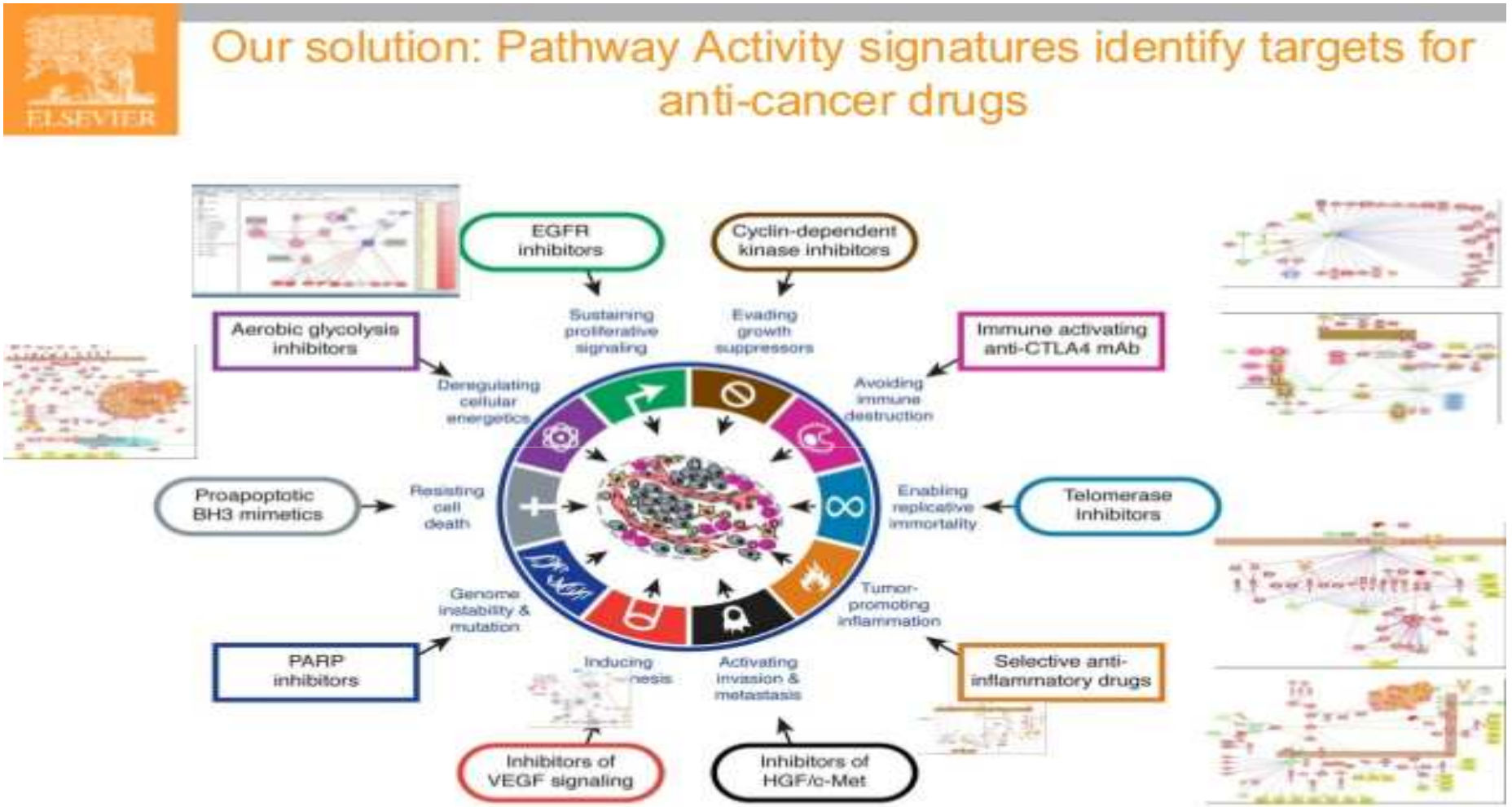
II Ogólnopolska Konferencja Naukowa
organizowana pod Patronatem Czasopisma

łącznie z II Turniejem Oddziałów Onkologii Klinicznej

Wyzwania onkologii spersonalizowanej i interdyscyplinarnej

10-11 maja 2019 roku, Warsaw Plaza Hotel, ul. Łączyny 5, 02-820 Warszawa

Kontakt: drrafals@wp.pl



Hanahan & Weinberg. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74

Thank you for your attention