Tratamiento en 1º línea de cáncer renal Avanzado: ¿hacia dónde vamos?

JAIME GARRE HERNANZ
F.E.A. UROLOGÍA
HOSPITAL UNIVERSITARIO DE MÉRIDA

‘’Hay una edad en la que se enseña lo que se sabe; pero inmediatamente viene otra en la que se enseña lo que no se sabe: eso se llama búsqueda’’ Roland Barthes

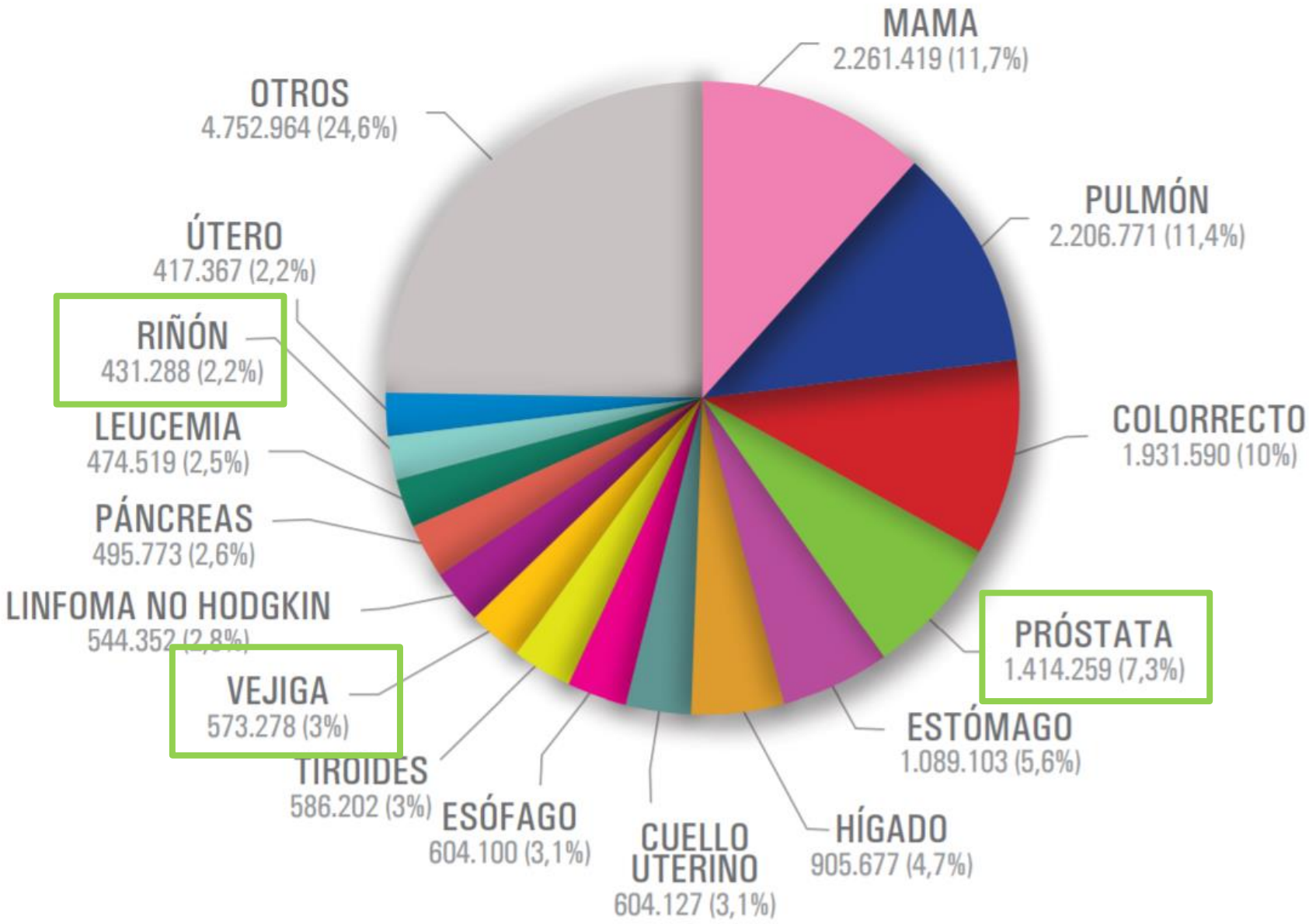
CÁNCER RENAL

- 5% hombre, y 3% en la mujer
- Hallazgo incidental: (ECO y TC) aumento de diagnósticos.
- Fc riesgo independientes: tabaco, obesidad e HTA. Diabetes?
- **Tras tto Qx: 40% desarrollarán enf MTX en función de T:**

  → **pT1: 0-7%**
  → **pT2: 5,3-26,5%**
  → **pT3: 26-52,8%**

Figura 2. Tumores más frecuentemente diagnosticados en el mundo. Estimación para el año 2020, ambos se

SEOM Sociedad Española de Oncología Médica



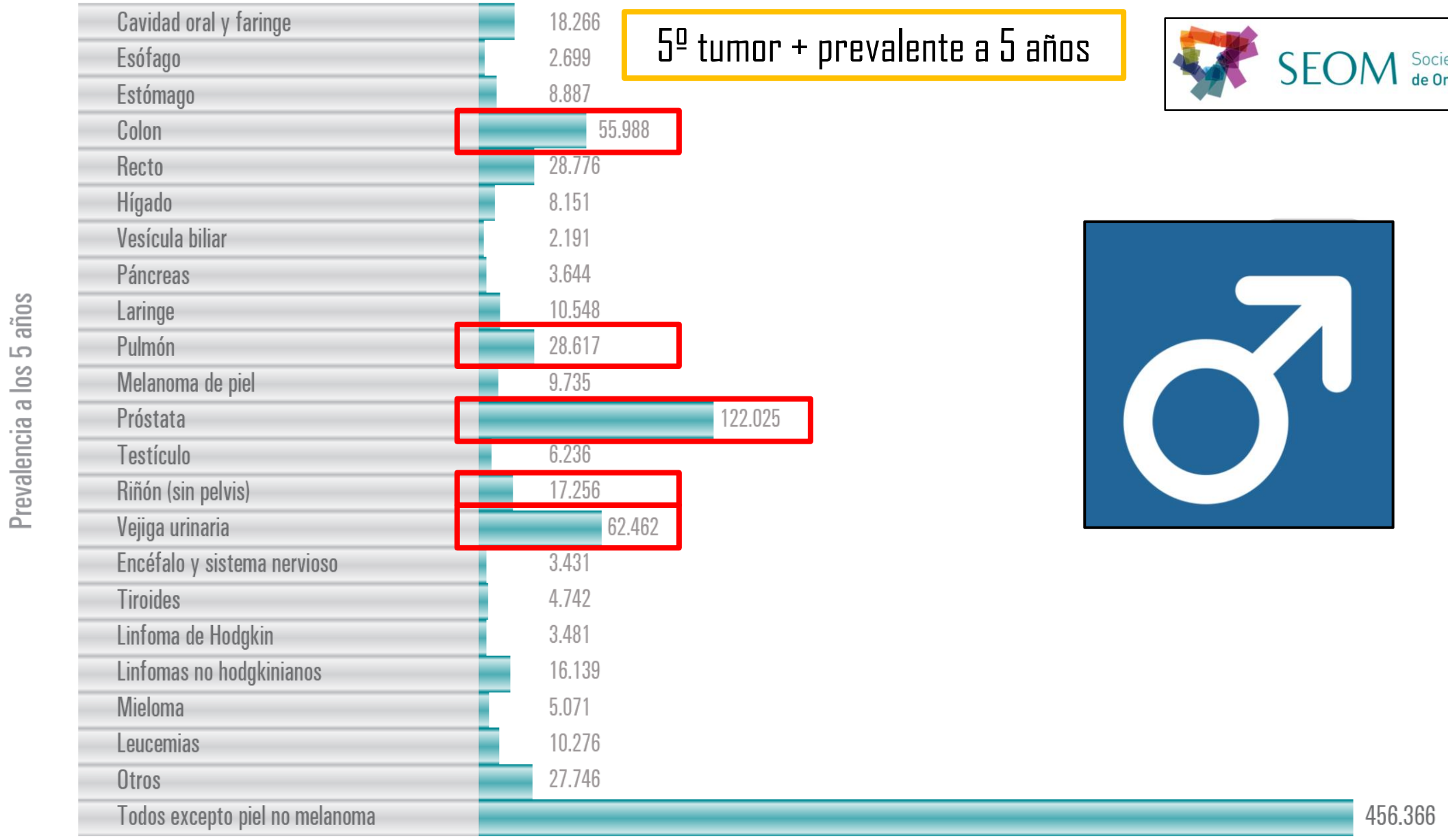
TOTAL: 19.292.789

14º en ambos Sexos

3º tumor Urológico + freq

Fuente: GLOBOCAN 2020, IARC

Figura 8. Estimación de la prevalencia a los 5 años de cánceres específicos en hombres en España para el año 2020.



Fuente: Red Española de Registros de Cáncer (REDECAN)

Nuevos casos de Ca. Renal Diagnosticados en España en 2020

8554

Type	Percentage of RCC (~)	Advanced disease at diagnosis (T3-4, N+, M+)
clear-cell RCC	80-90%	28%
papillary RCC	6-15%	17.6%
chromophobe RCC	2-5%	16.9%

International Agency for Research on Cancer

World Health Organization

21. Keegan, K.A., et al. Histopathology of surgically treated renal cell carcinoma: survival differences by subtype and stage. J Urol, 2012. 188: 391.

Nuevos casos de Ca. R
Diagnosticados en España

8554

Type	Percentage of RCC (~)	Advanced disease at diagnosis (T3-4, N+, M+)
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papillary RCC	6-15%	17.6%
chromophobe RCC	2-5%	16.9%

→Enfermedad localizada: 62-65% de los pacientes

→Afectación regional (ganglios): 17% de los pacientes.

→Enfermedad metastática: 17% de los pacientes

International Agency for Research on Cancer

World Health Organization

T - Primary Tumour

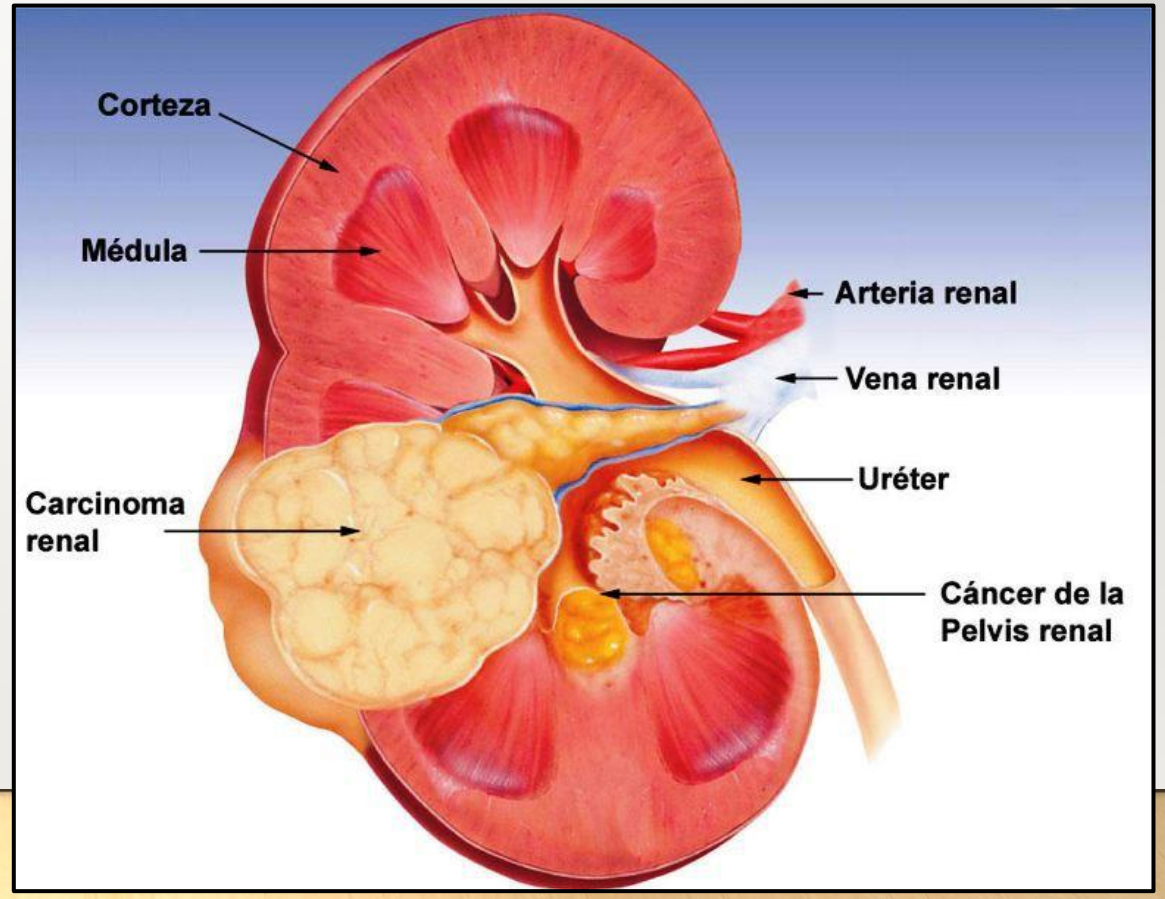
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤ 7 cm or less in greatest dimension, limited to the kidney
T1a	Tumour ≤ 4 cm or less
T1b	Tumour > 4 cm but ≤ 7 cm
T2	Tumour > 7 cm in greatest dimension, limited to the kidney
T2a	Tumour > 7 cm but ≤ 10 cm
T2b	Tumours > 10 cm, limited to the kidney
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia
T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumour invades perirenal and/or renal sinus fat (peripelvic fat), but not beyond Gerota fascia
T3b	Tumour grossly extends into the vena cava below diaphragm
T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)

N - Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

M - Distant Metastasis

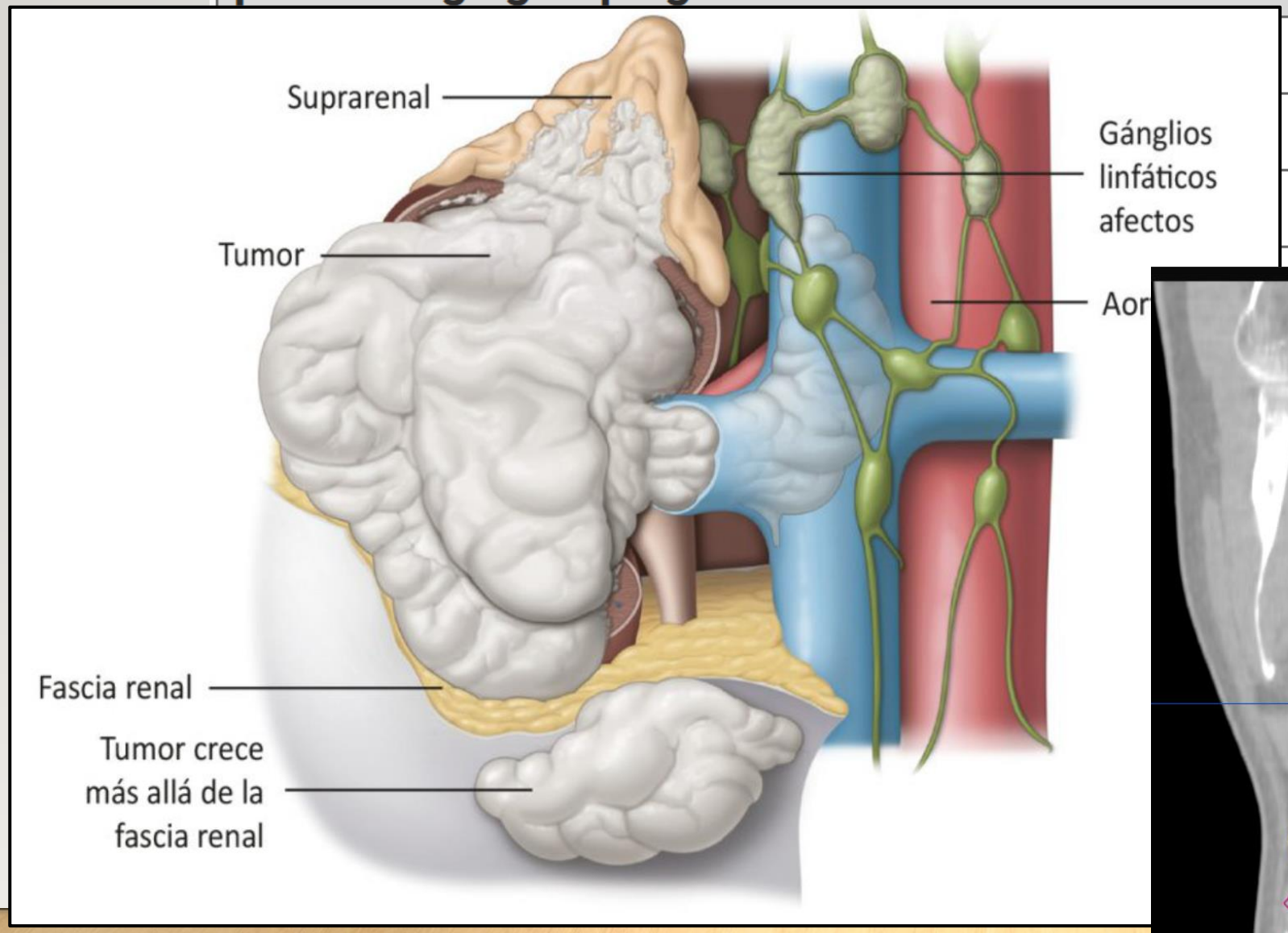
M0	No distant metastasis
M1	Distant metastasis

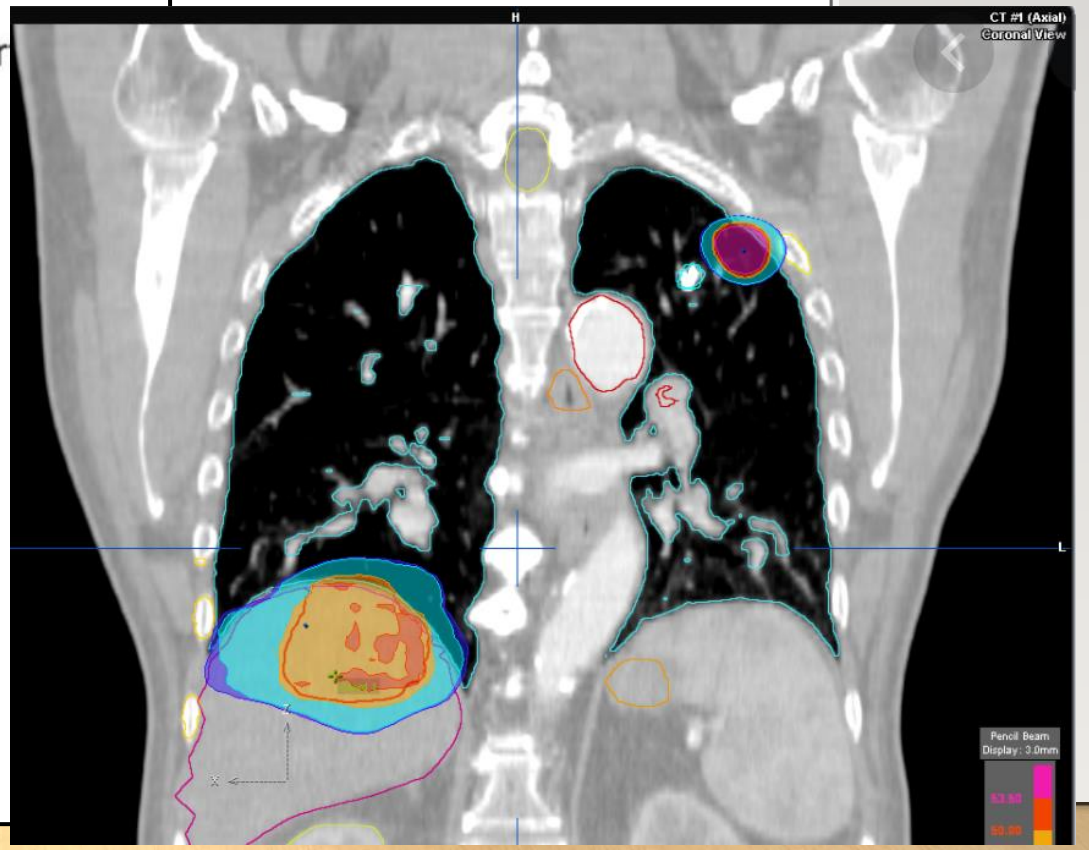


European Association of Urology

pTNM stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

pTNM stage grouping





VOLUME 27 · NUMBER 34 · DECEMBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prognostic Factors for Overall Survival in Patients With Metastatic Renal Cell Carcinoma Treated With Vascular Endothelial Growth Factor–Targeted Agents: Results From a Large, Multicenter Study

Daniel Y.C. Heng, Wanling Xie, Meredith M. Regan, Mark A. Warren, Ali Reza Golshayan, Chakshu Sahi, Bernhard J. Eigl, J. Dean Ruether, Tina Cheng, Scott North, Peter Venner, Jennifer J. Knox, Kim N. Chi, Christian Kollmannsberger, David F. McDermott, William K. Oh, Michael B. Atkins, Ronald M. Bukowski, Brian I. Rini, and Toni K. Choueiri

MSKCC (Memorial Sloan-Kettering Cancer Center)

Validar los Factores de mal Px que disminuyen supervivencia global previo al inicio de tto

Prognostic Factors for Overall Survival in Patients With Metastatic Renal Cell Carcinoma Treated With Vascular Endothelial Growth Factor–Targeted Agents: Results From a Large, Multicenter Study

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MSKCC risk factor	
Karnofsky performance status <80%	
Lactate dehydrogenase >1.5 × ULN (Normal: 140 U/L)	
Hemoglobin <LLN (Normal men: 13.5-17.5 g/dL; normal women: 12.0-15.5 g/dL)	
Corrected serum calcium >10 mg/dL (>2.5 mmol/L)	
Time from diagnosis to treatment <1 year	
Risk group	**Number of factors**
Favorable	0
Intermediate	1–2
Poor	3–5

Prognostic Factors for Overall Survival in Patients With Metastatic Renal Cell Carcinoma Treated With Vascular Endothelial Growth Factor–Targeted Agents: Results From a Large, Multicenter Study

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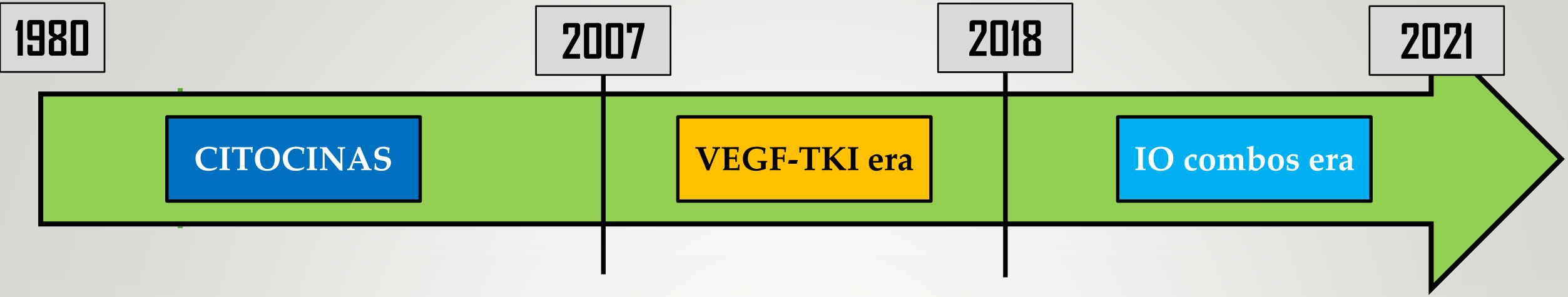
Risk group	**tors**
Favorable	0
Intermediate	1–2
Poor	3–5

PLAQUETAS

NEUTRÓFILOS

The Metastatic Renal Cancer Database Consortium (IMDC) risk model

Risk factors**	Cut-off point used
Karnofsky performance status	< 80%
Time from diagnosis to treatment	< 12 months
Haemoglobin	< Lower limit of laboratory reference range
Corrected serum calcium	> 10.0 mg/dL (2.4 mmol/L)
Absolute neutrophil count (neutrophilia)	> upper limit of normal
Platelets (thrombocytosis)	> upper limit of normal


1980
2007
2018
2021
CITOCINAS
VEGF-TKI era
IO combos era

1980

2007

2018

2021

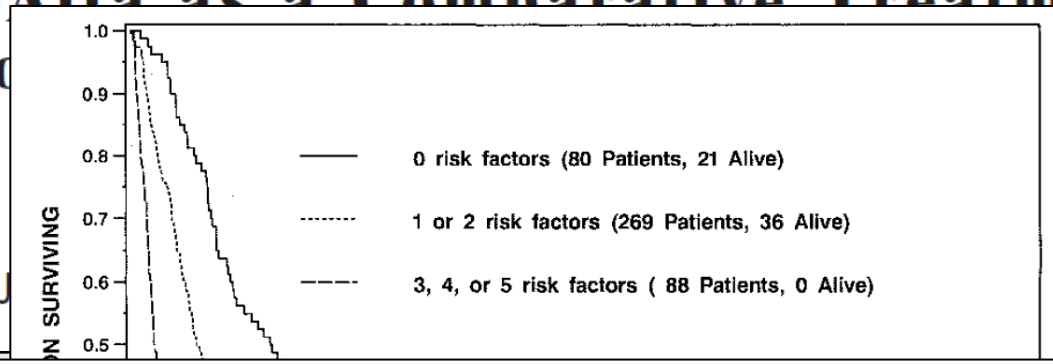
CITOCINAS

VEGF-TKI era

IO combos era

Interferon-Alfa as a Comparative Treatment for Clinical Trials of Advanced Renal

By Robert J … Madh…



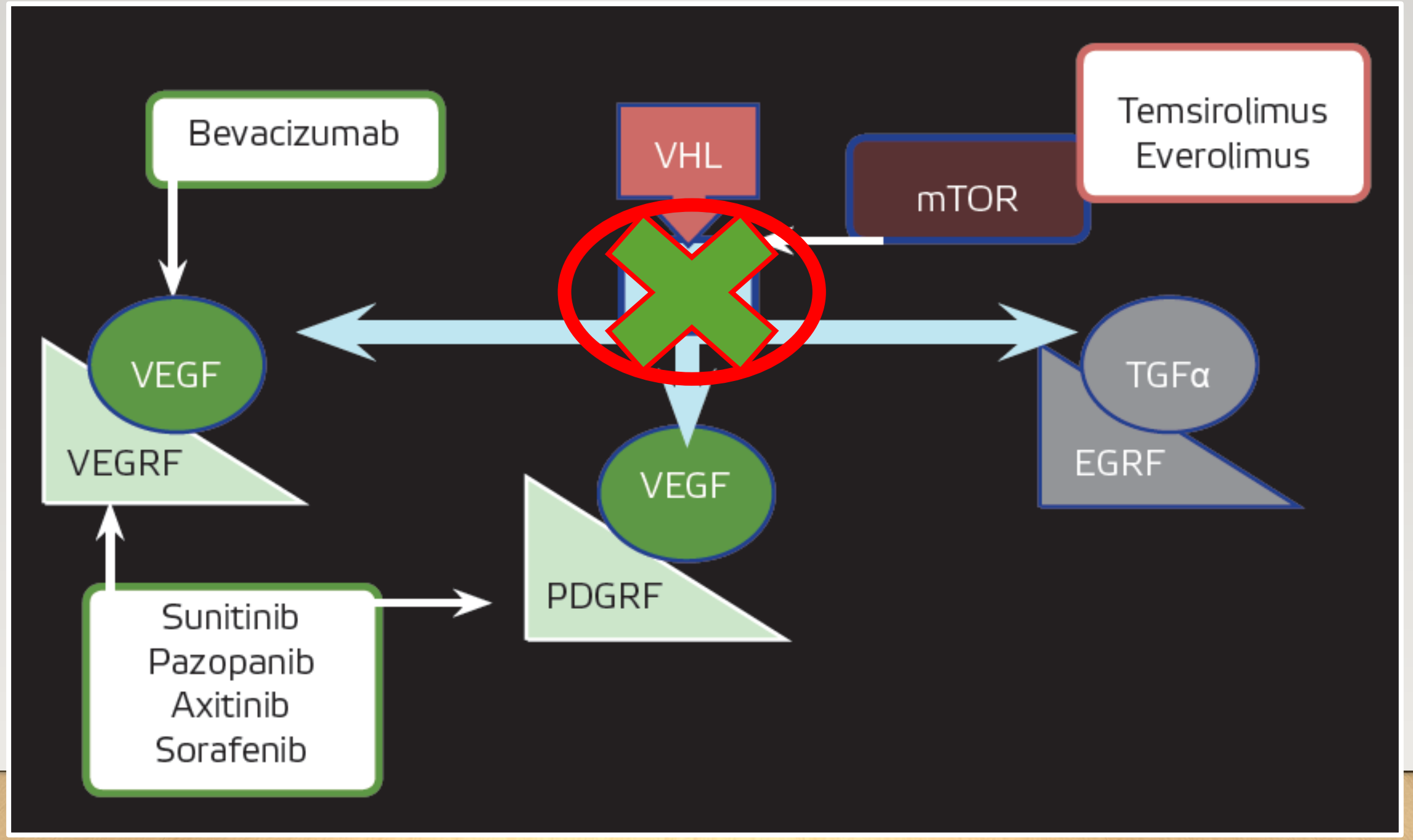
Mediana respuesta 13.8 meses para grupo intermedio

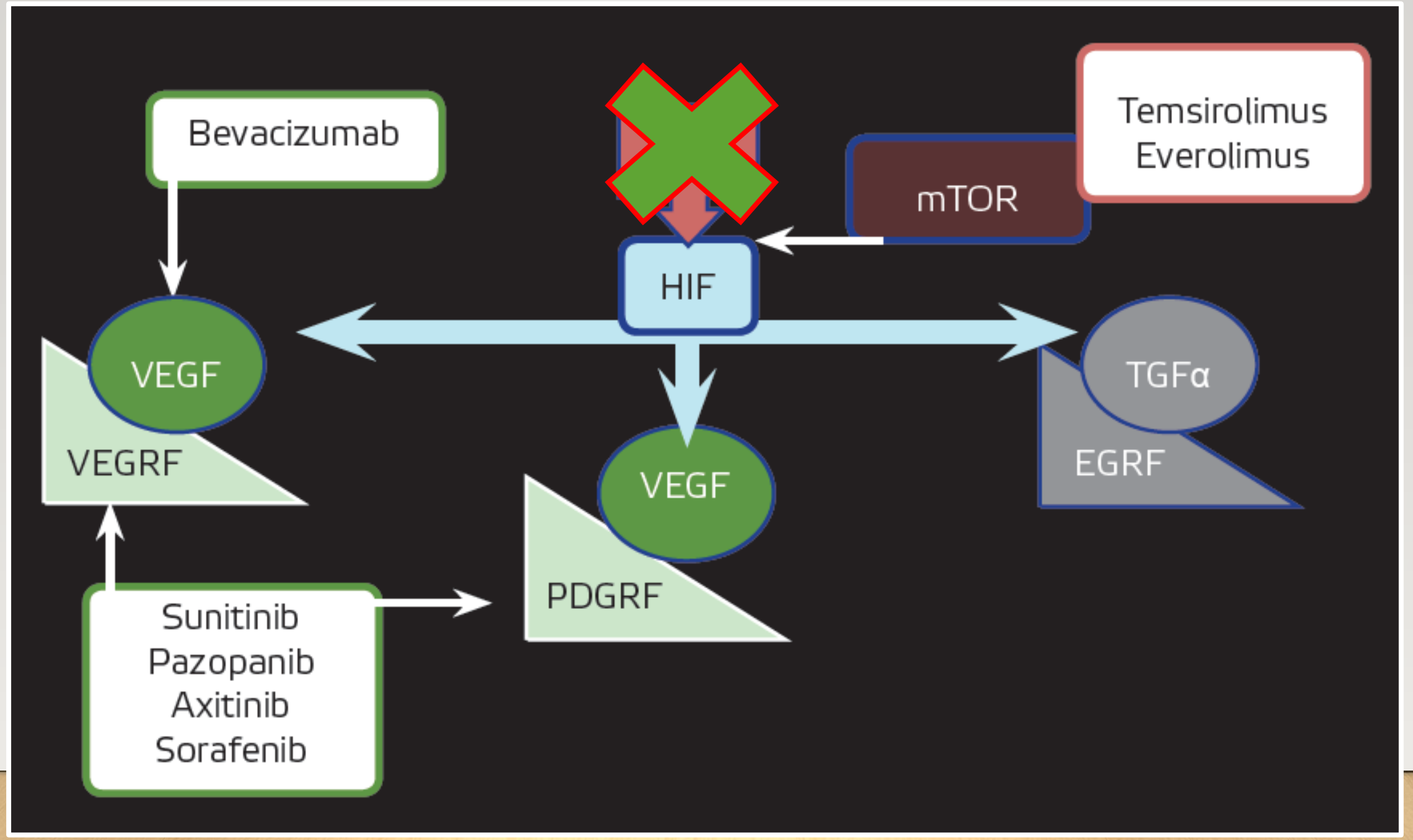
Table 7. Results According to Risk Factors

No. of Risk Factors	%*	Alive (%)	Survival (months)		1-Year Survival (%)	3-Year Survival (%)
			Median	95% CI		
0	18	26	29.6	20.9, 37.8	83	45
1 or 2	62	13	13.8	12.4, 15.9	58	17
3, 4, or 5	20	0	4.9	4.3, 6.3	20	2

*N = 437; 26 patients are missing one or more of the five risk factors.

who were missing one or more of the five risk factors were excluded. | indicates last follow-up.


Bevacizumab
VHL
mTOR
Temsirolimus
Everolimus
VEGF
VEGRF
TGFα
EGRF
VEGF
PDGRF
Sunitinib
Pazopanib
Axitinib
Sorafenib


Bevacizumab
Temsirolimus
Everolimus
mTOR
HIF
VEGF
VEGRF
VEGF
PDGRF
TGFα
EGRF
Sunitinib
Pazopanib
Axitinib
Sorafenib

1980 | 2007 | 2018 | 2021

CITOCINAS | VEGF-TKI era | IO combos era

The N
JOURN

ESTABLISHED IN 1812

Sunitinib ve

Robert J. Motzer, M.D., Thomas E. Hu
Ronald M. Bukowski, M.D., Olivier R
Cezary Szczylik, M.D., Ph
Charles M

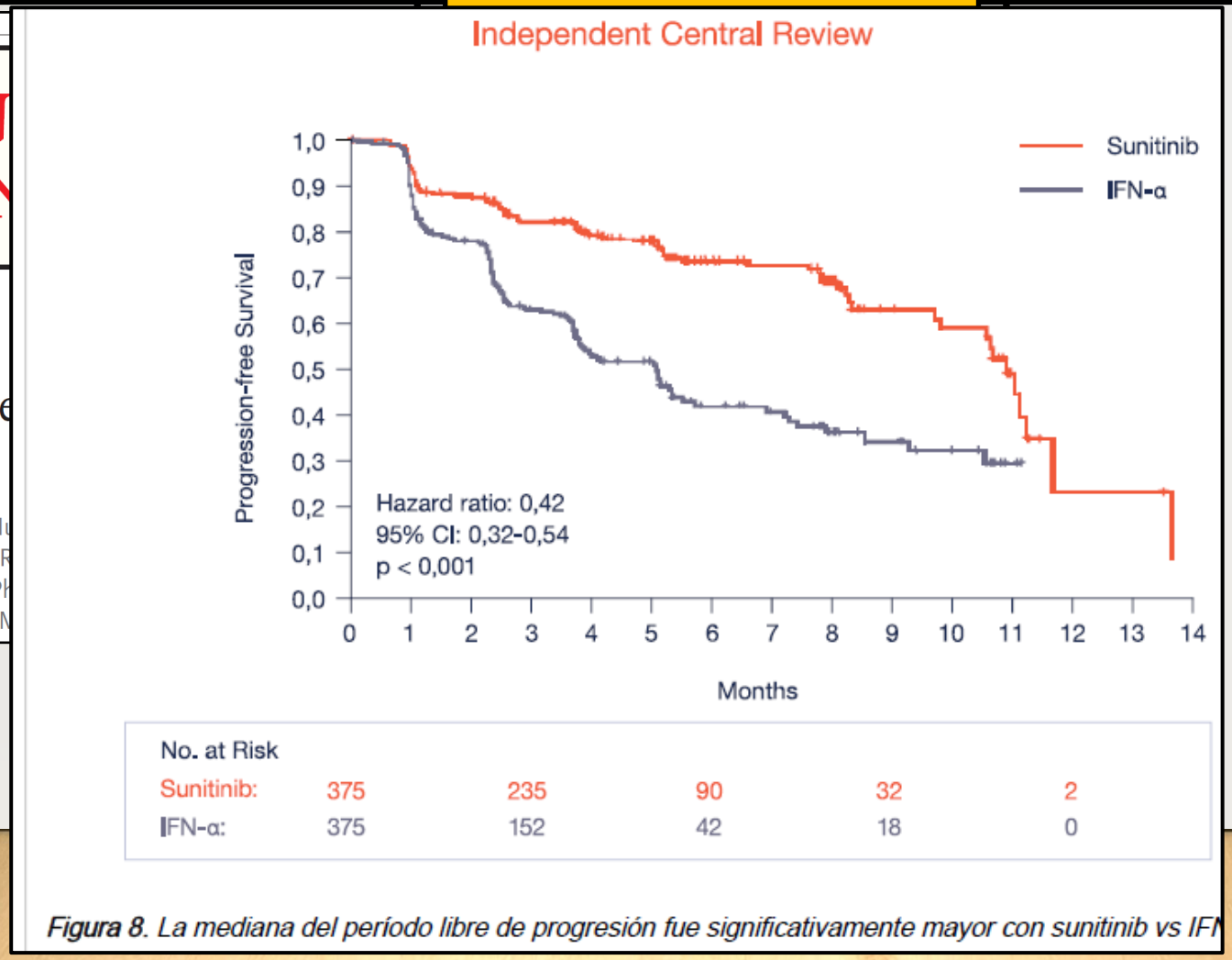


Figura 8. La mediana del período libre de progresión fue significativamente mayor con sunitinib vs IF

SLP (PFS):11 vs 5 meses.
Hr: 0,42

1980 | 2007 | 2018 | 2021

CITOCINAS | VEGF-TKI era | IO combos era

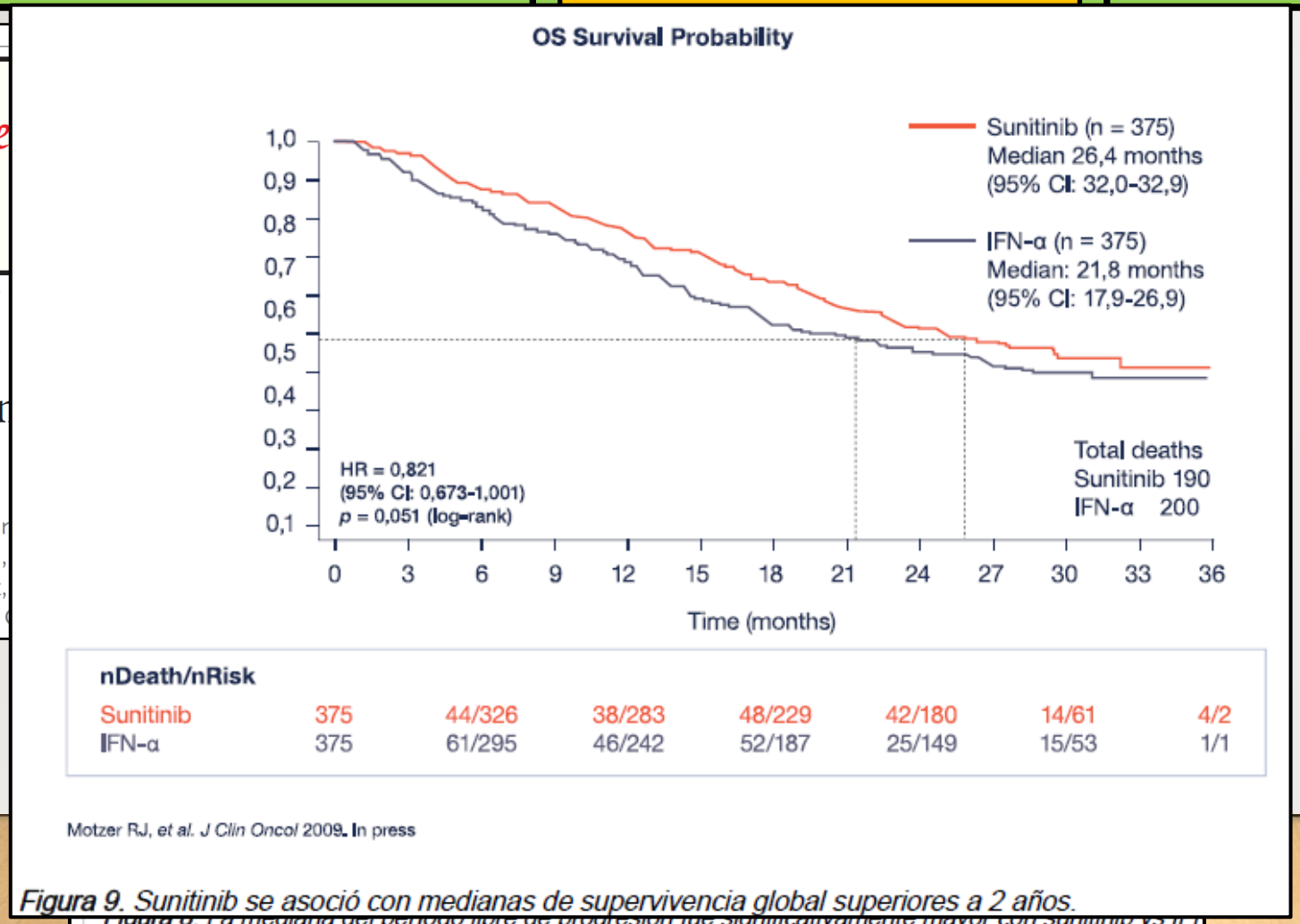


Figura 9. Sunitinib se asoció con medianas de supervivencia global superiores a 2 años.

SG: 26,4 vs 21,8 meses.

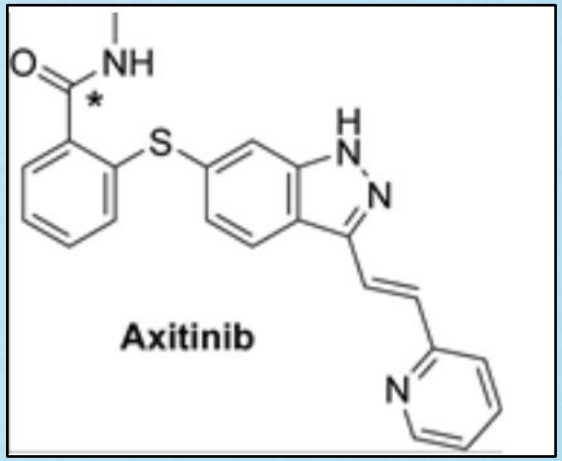
2005: TERAPIA DIRIGIDA ANTIANGIOGÉNICOS

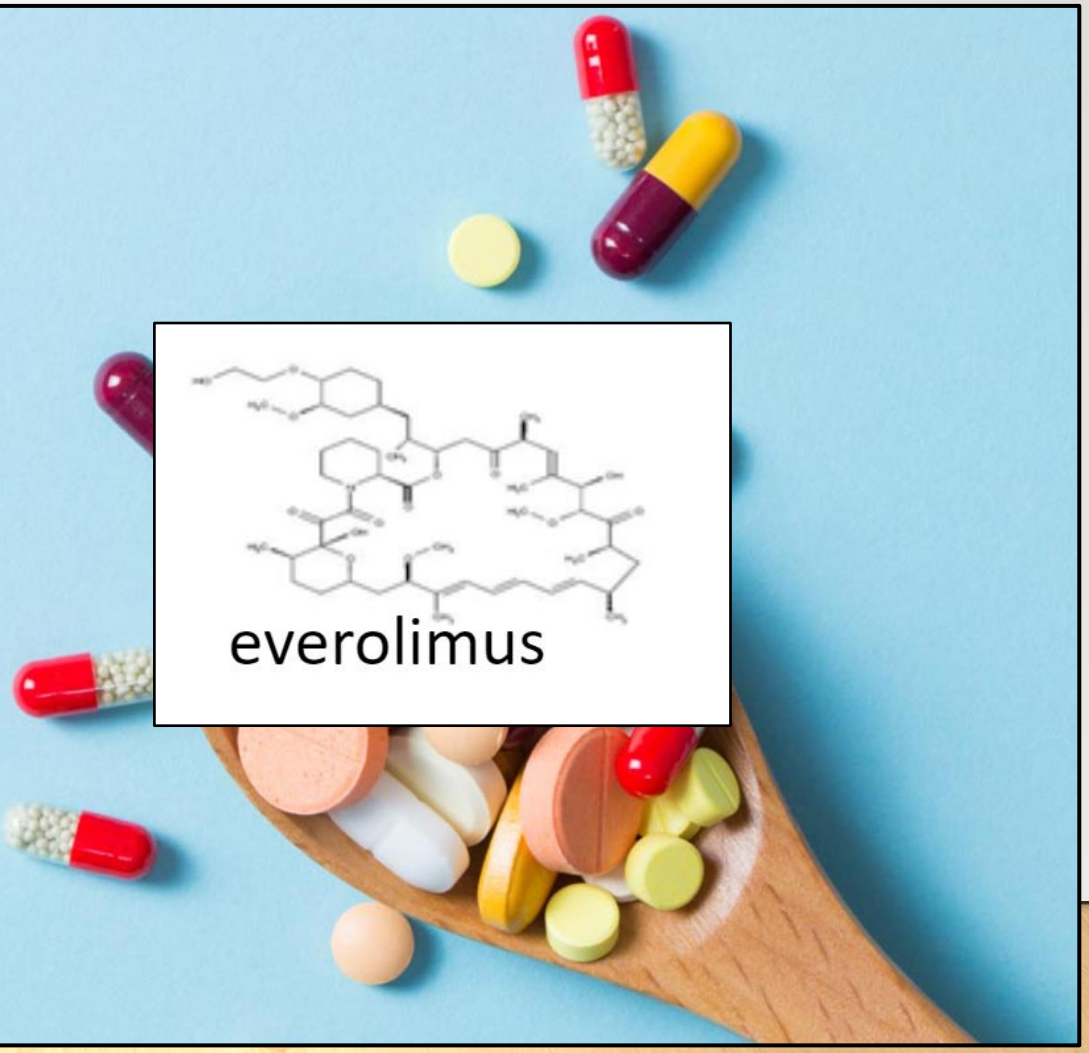
2007

Sorafenib

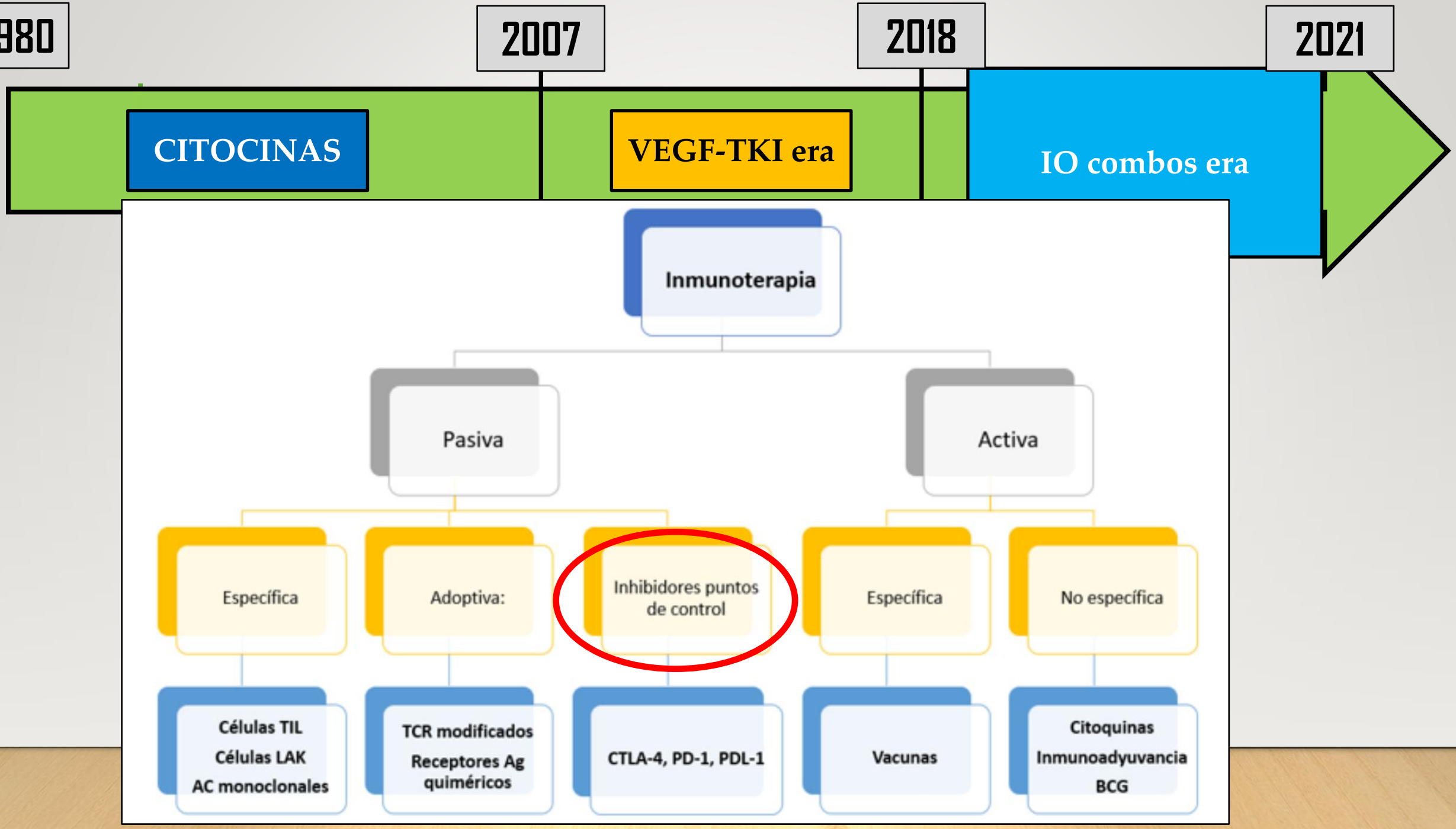
Sunitinib

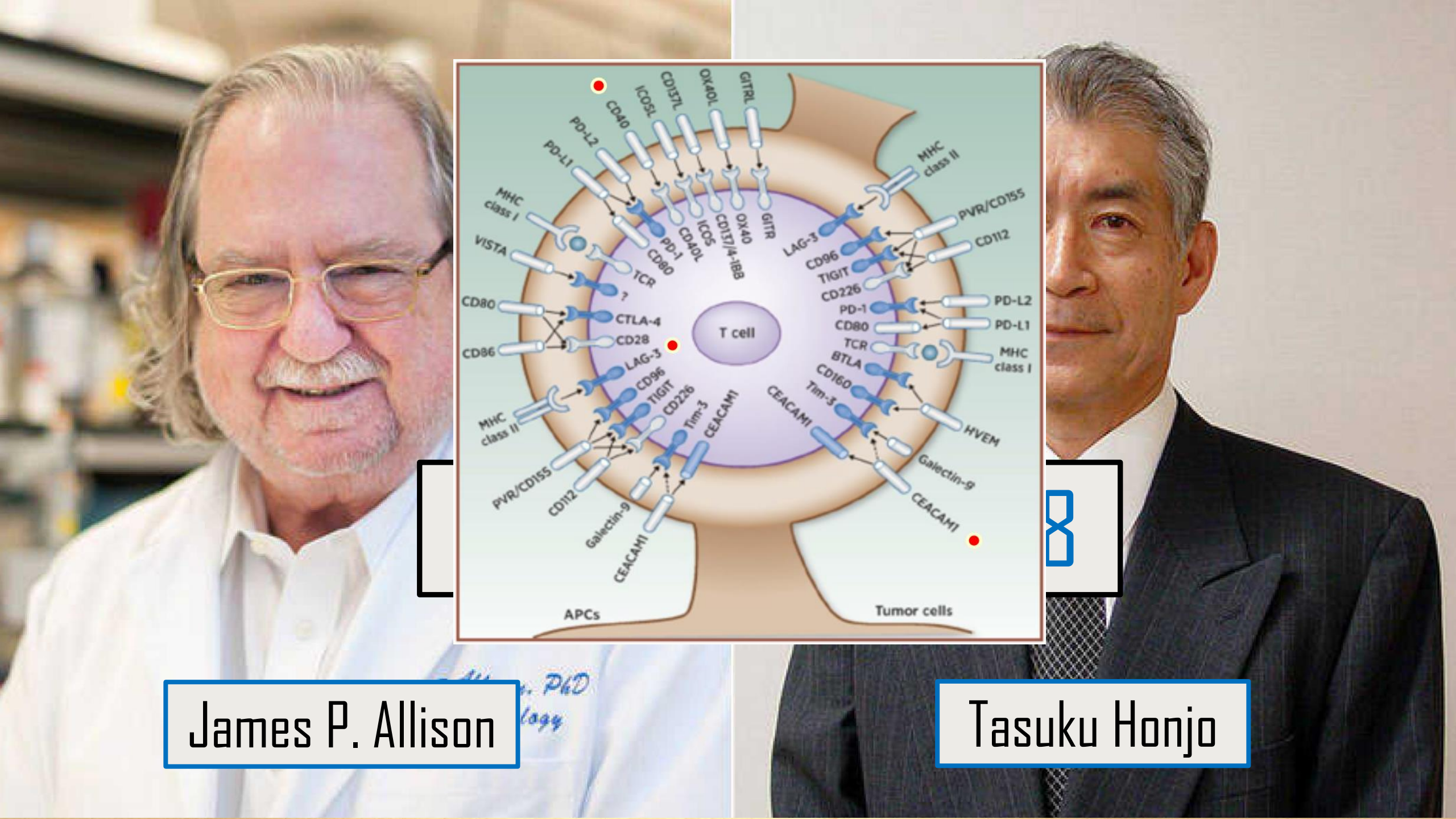
Pazopanib

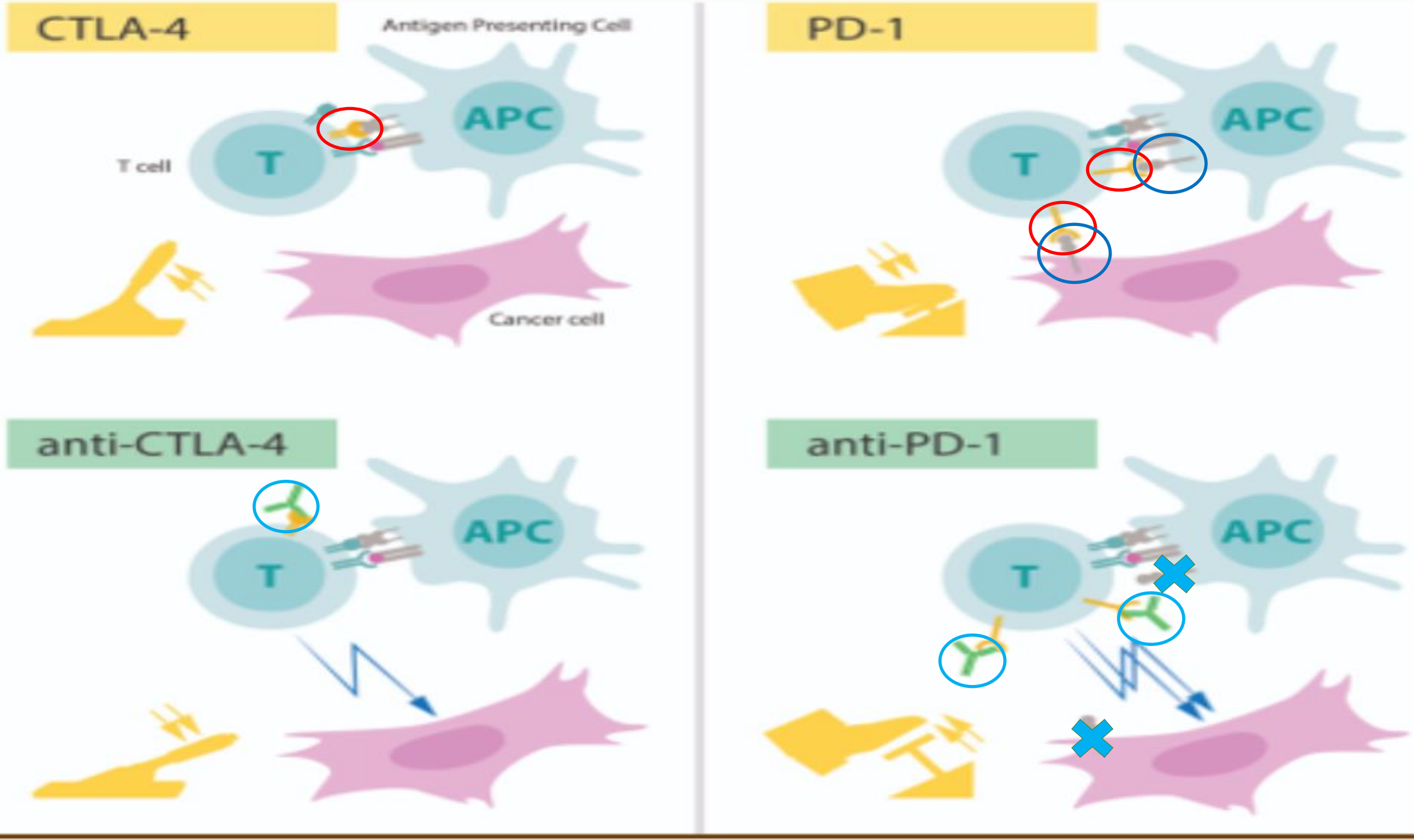





10
ROLAND GARROS
PARIS


1980
2007
2018
2021
CITOCINAS
VEGF-TKI era
IO combos era
Inmunoterapia
Pasiva
Activa
Específica
Adoptiva:
Inhibidores puntos de control
Específica
No específica
Células TIL
Células LAK
AC monoclonales
TCR modificados
Receptores Ag quiméricos
CTLA-4, PD-1, PDL-1
Vacunas
Citoquinas
Inmunoadyuvancia
BCG


James P. Allison
Tasuku Honjo
T cell
APCs
Tumor cells
CD40
ICOSL
CD137L
OX40L
GITRL
PD-L2
PD-L1
MHC class I
VISTA
CD80
CD86
MHC class II
PVR/CD155
CD112
Galectin-9
CEACAM1
PD-1
CD40L
ICOS
CD137/4-1BB
OX40
GITR
TCR
CTLA-4
CD28
LAG-3
CD96
TIGIT
CD226
Tim-3
BTLA
CD160
HVEM


CTLA-4
Antigen Presenting Cell
APC
T cell
T
Cancer cell
PD-1
APC
T
anti-CTLA-4
APC
T
anti-PD-1
APC
T

ANTICUERPOS MONOCLONALES QUE BLOQUEAN:

Receptor inhibidor de PD-1

- NIVOLUMAB
- PEMBROLIZUMAB

Antígeno 4 ligado al LT citotóxico (CTLA-4)

- IPILIMUMAB

Ligando PD-1: PD-L1

- ATEZOLIZUMAB
- AVELUMAB


Futuro
Presente
Pasado


HE DADO EN EL CLAVO
Y LO SABES!
memegenerator.es

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, F. Donskov, V. [illegible] rney, R. Hawkins, A. Ravaud, M [illegible], D. Castellano, B.I. Rini, A.C. Ch [illegible] Doan, P. Sharma, H.J. Hammers, and B. Escudier, for the CheckMate 214 Investigators*

CHECKMATE 214

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

B.I. Rini, E.R. Plimack, V. Stus, R. Gafanov, R. Hawkins, D. Nosov, F. Pouliot, B. Alekseev, D. S [illegible] anivska, [illegible] enko [illegible] arkus, J. B [illegible] u, R.F. Perini, Atkins, and T. Powles, for the KEYNOTE-426 Investigators*

KEYNOTE-426

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Avelumab plus Axitinib versus [illegible]nitinib for Advanced Renal-Cell Carcinoma

Robert J. Motzer, M.D., Konstantin Penkov, M.D., Ph.D., John Haanen, Ph.D., Brian Rini, M. [illegible] ampbell, M.D., Balaj [illegible] M.D., Sylvie [illegible], Ph.D., Jae L. Lee, M.D., [illegible]r, Jr., M.D., Ph.D., Howard Gurney, M.D., Manuela Schmidinger, M.D., James Larkin, M.D., Ph.D., Michael B. Atkins, M.D., Jens Bedke, M.D., Boris Alekseev, M.D., Jing Wang, Ph.D., Mariangela Mariani, Ph.D., Paul B. Robbins, Ph.D., Aleksander Chudnovsky, M.D., Camilla Fowst, M.D., Subramanian Hariharan, M.D., Bo Huang, Ph.D., Alessandra di Pietro, M.D., Ph.D., and Toni K. Choueiri, M.D.

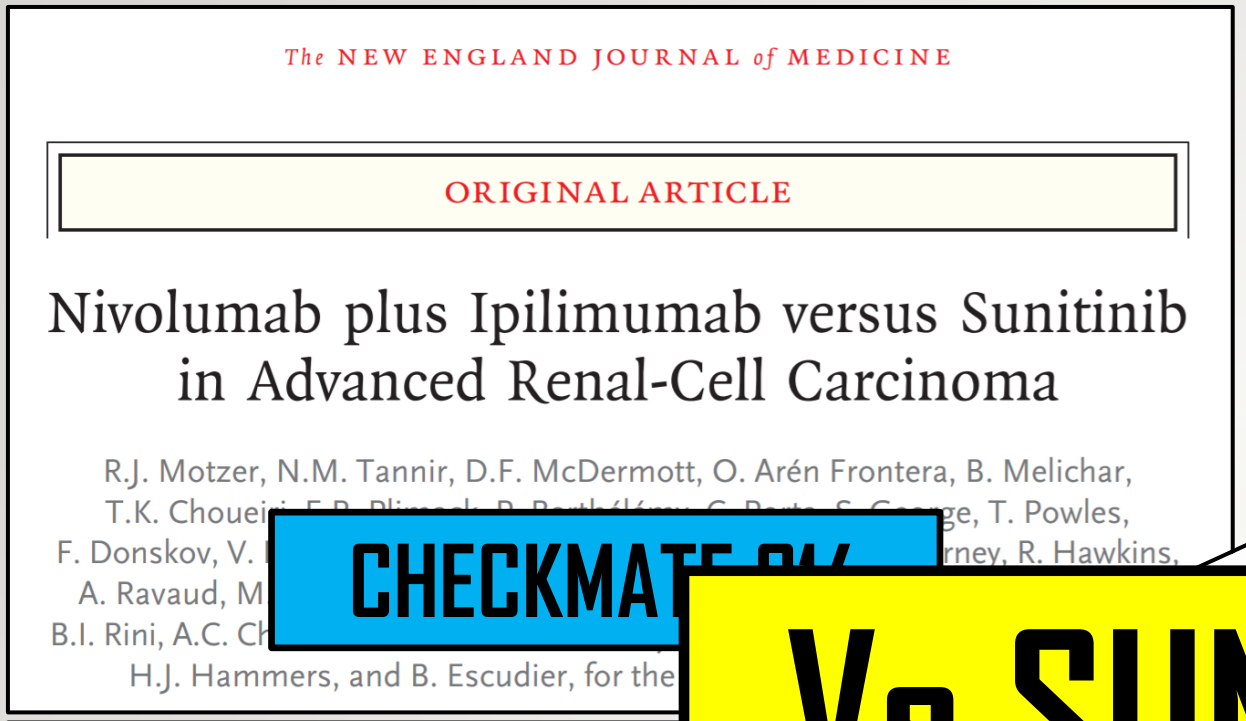
JAVELIN 101

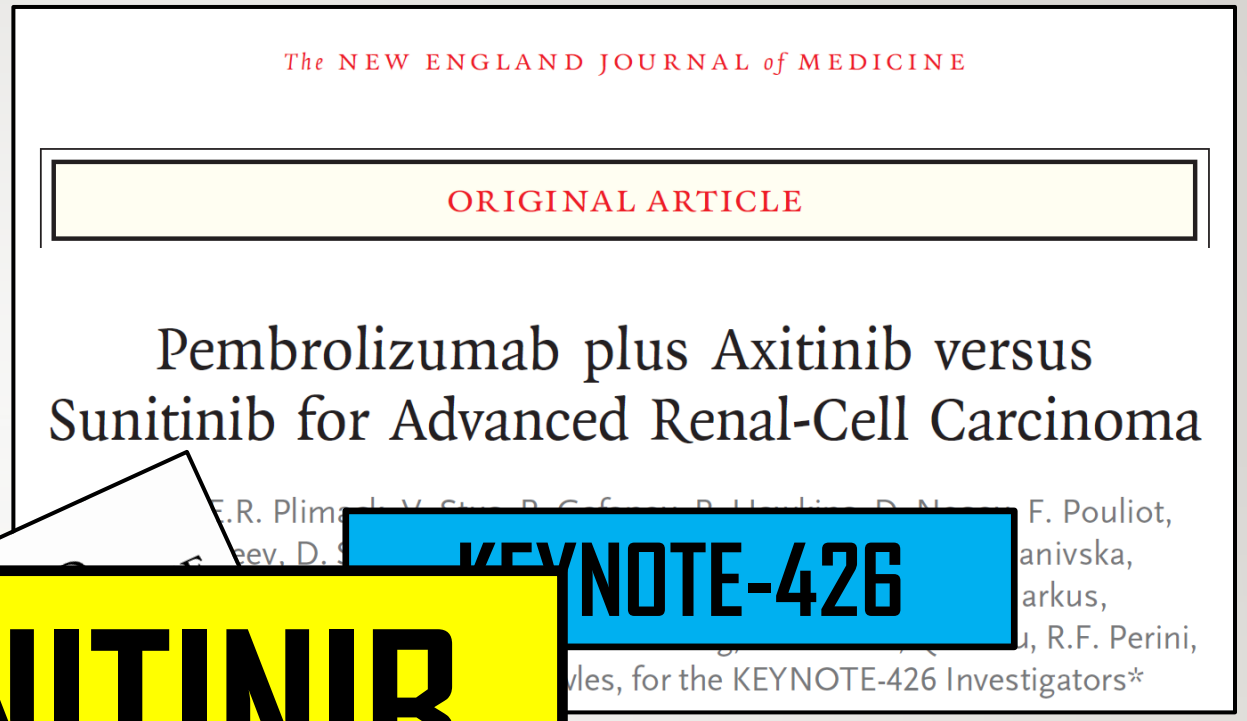
The NEW ENGLAND JOURNAL of MEDICINE

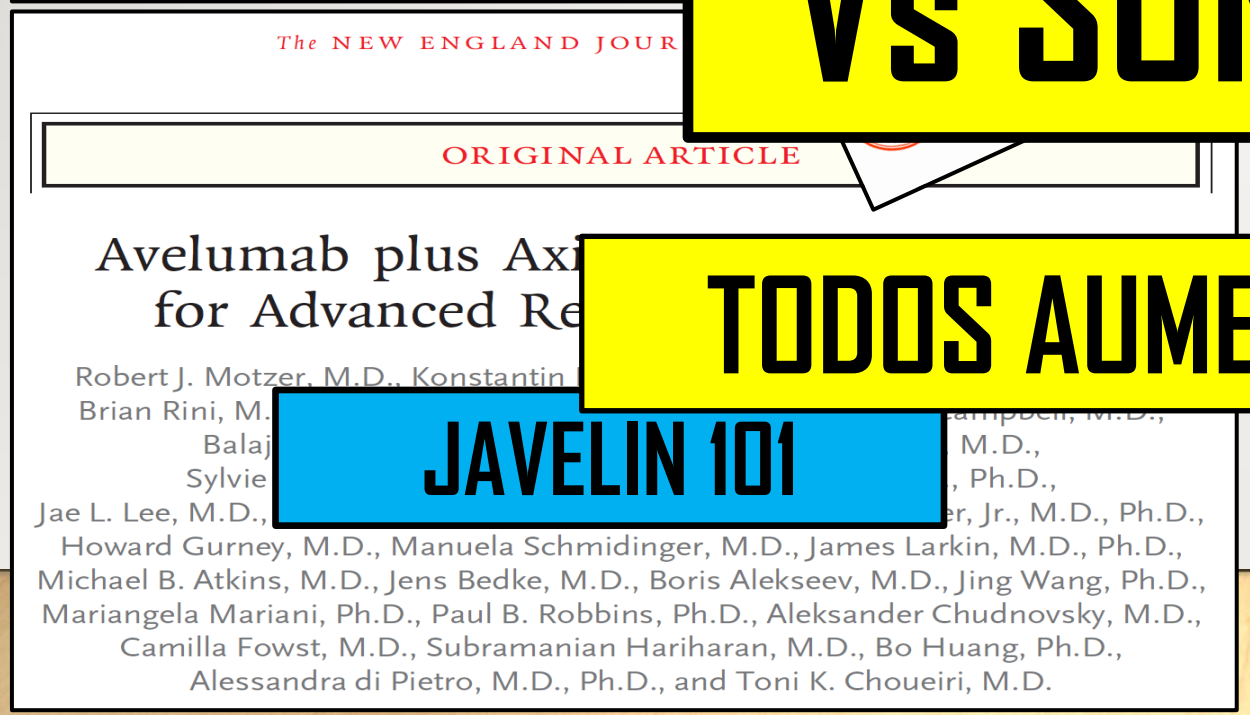
Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial

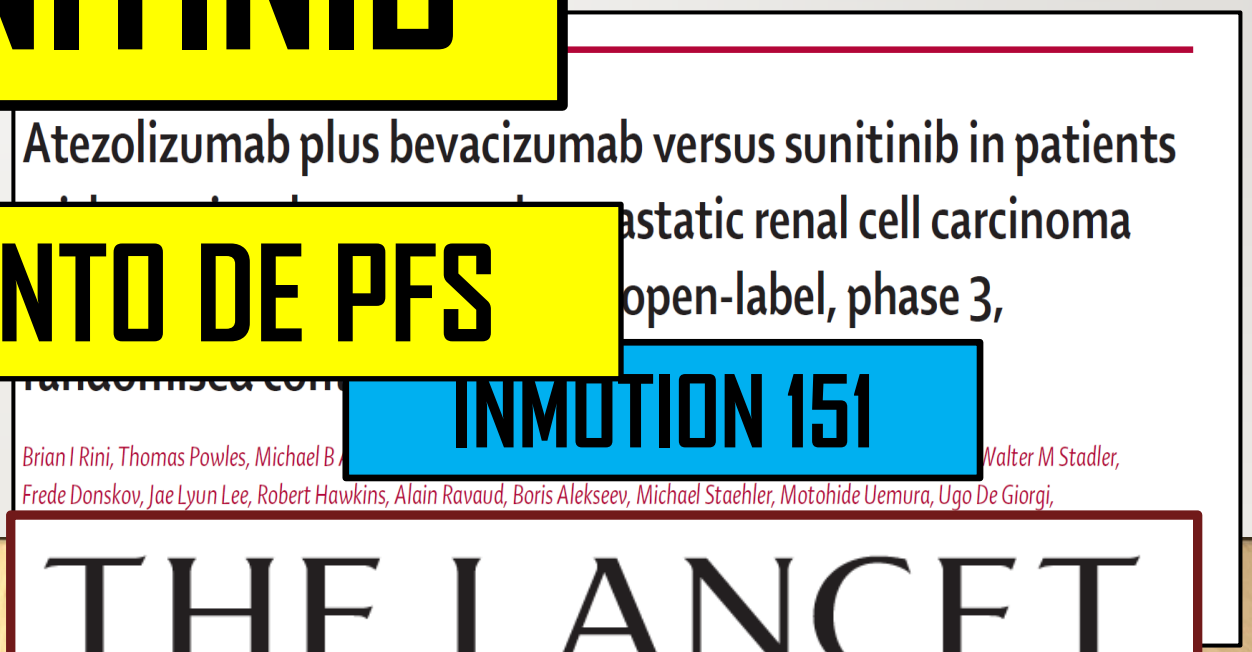
INMOTION 151

THE LANCET









CHECKMATE

KEYNOTE-426

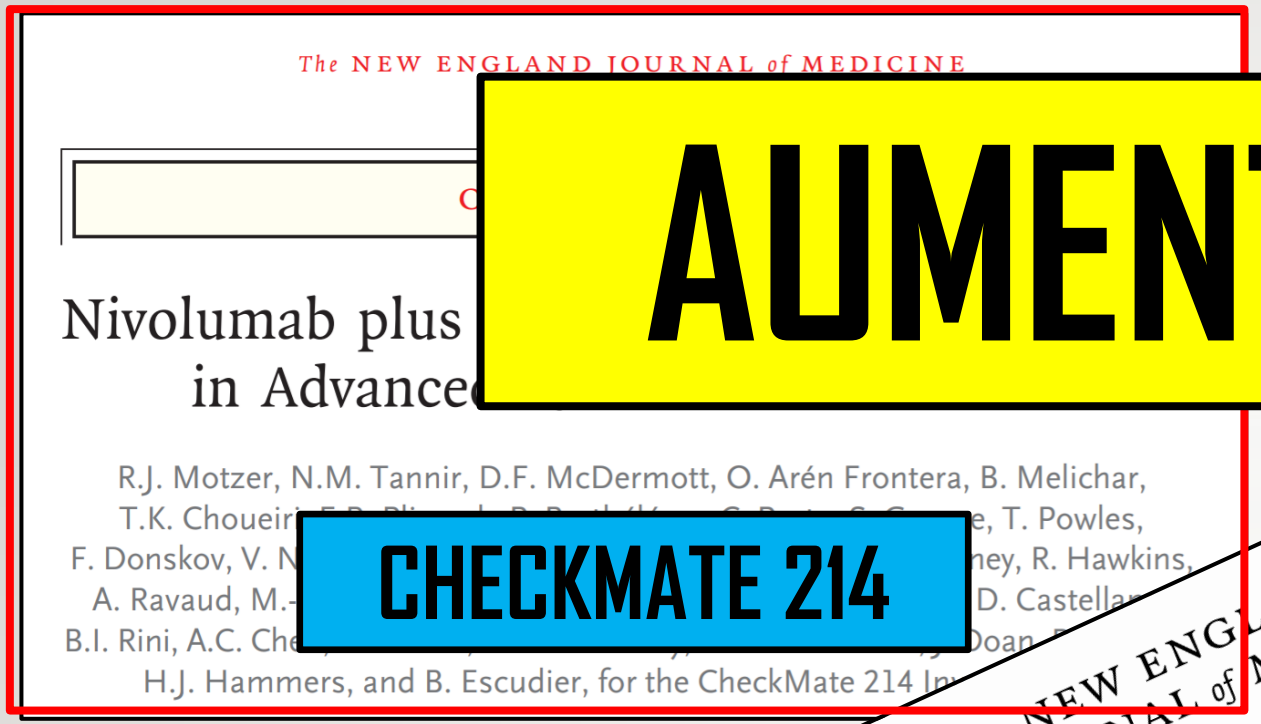
Vs SUNITINIB

TODOS AUMENTO DE PFS

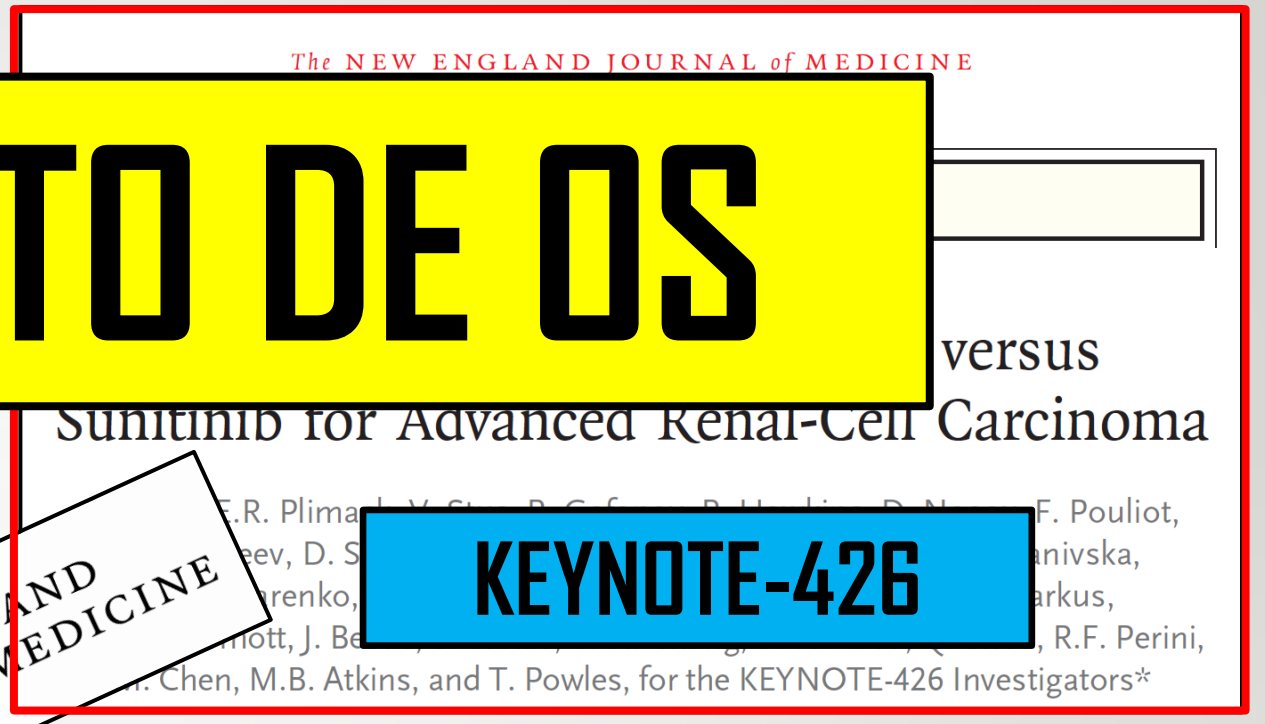
JAVELIN 101

INMOTION 151

AUMENTO DE OS



CHECKMATE 214



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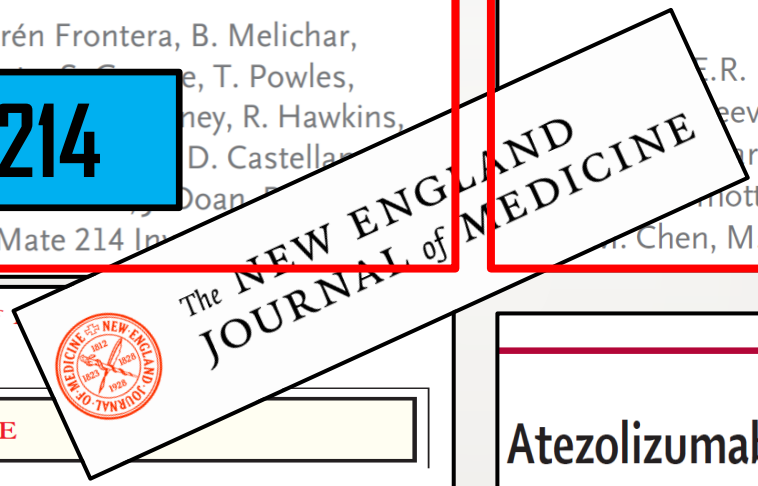

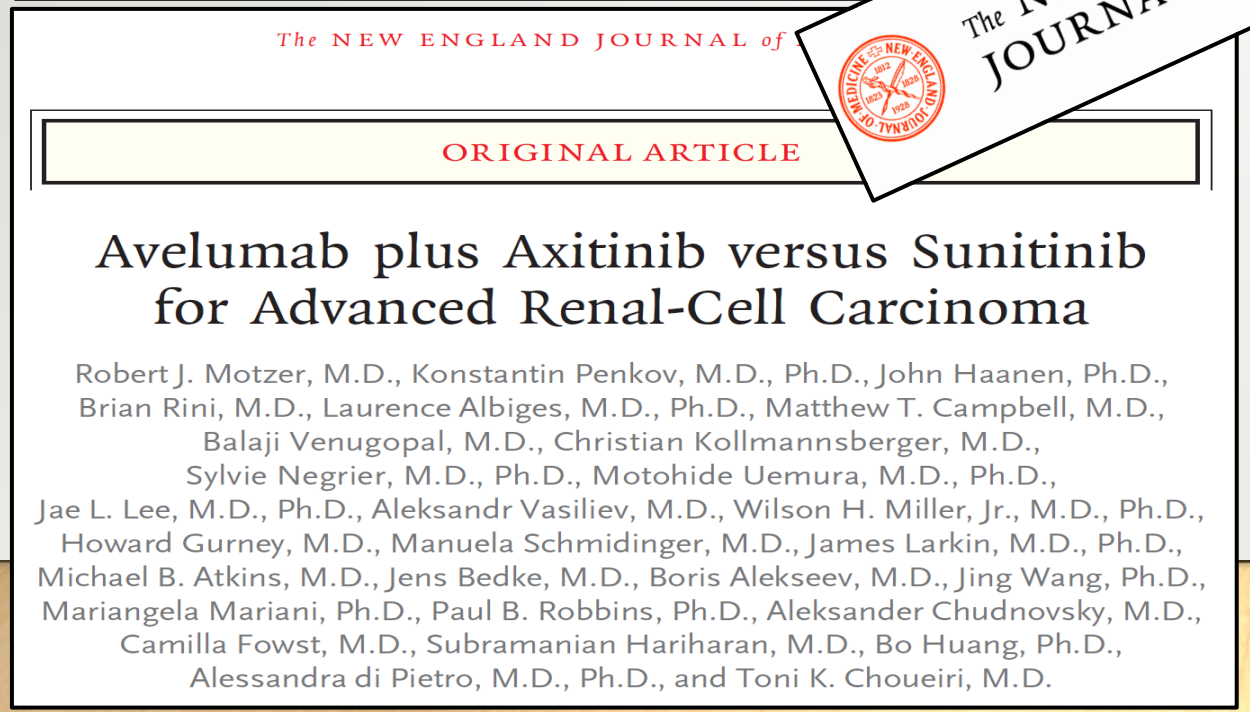

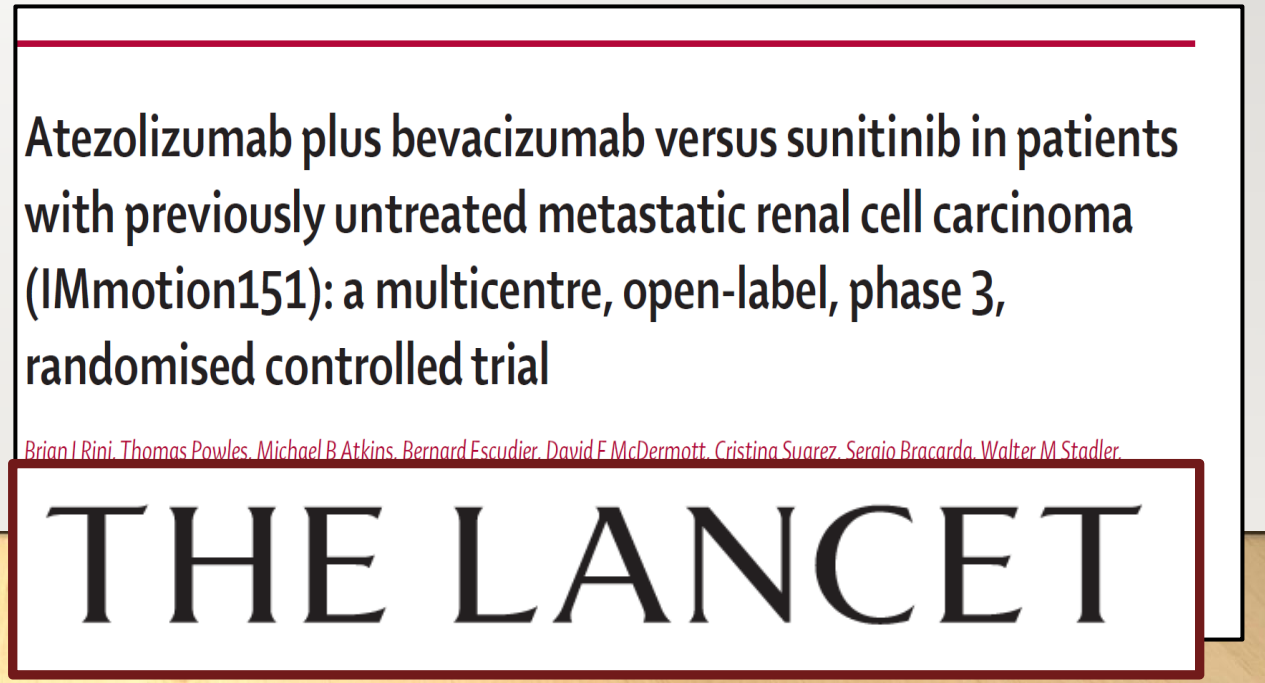

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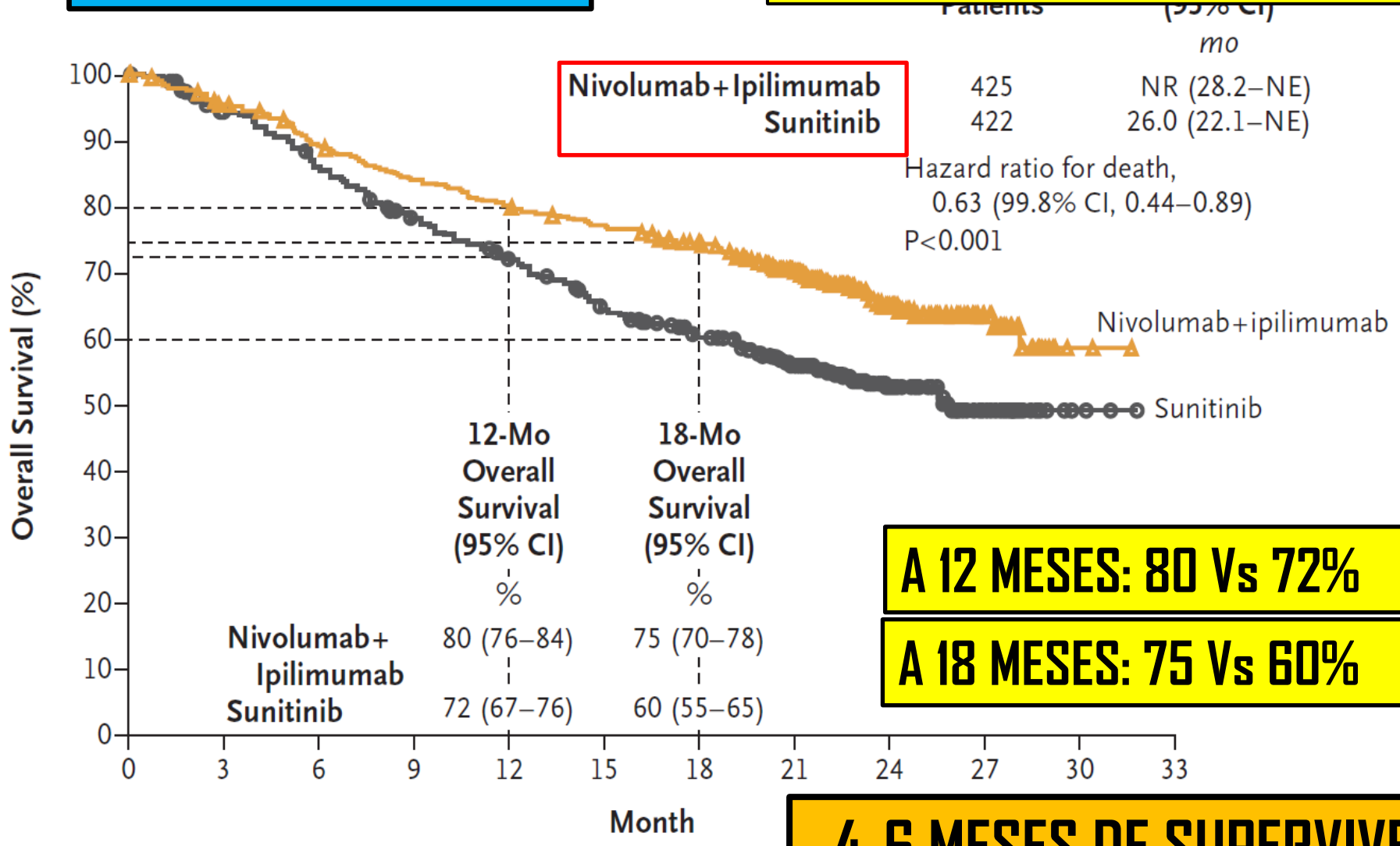
CHECKMATE 214

CHECKMATE 214

GRUPOS INTERMEDIO Y POBRE IMDC



OS

8%

15%

A 12 MESES: 80 Vs 72%

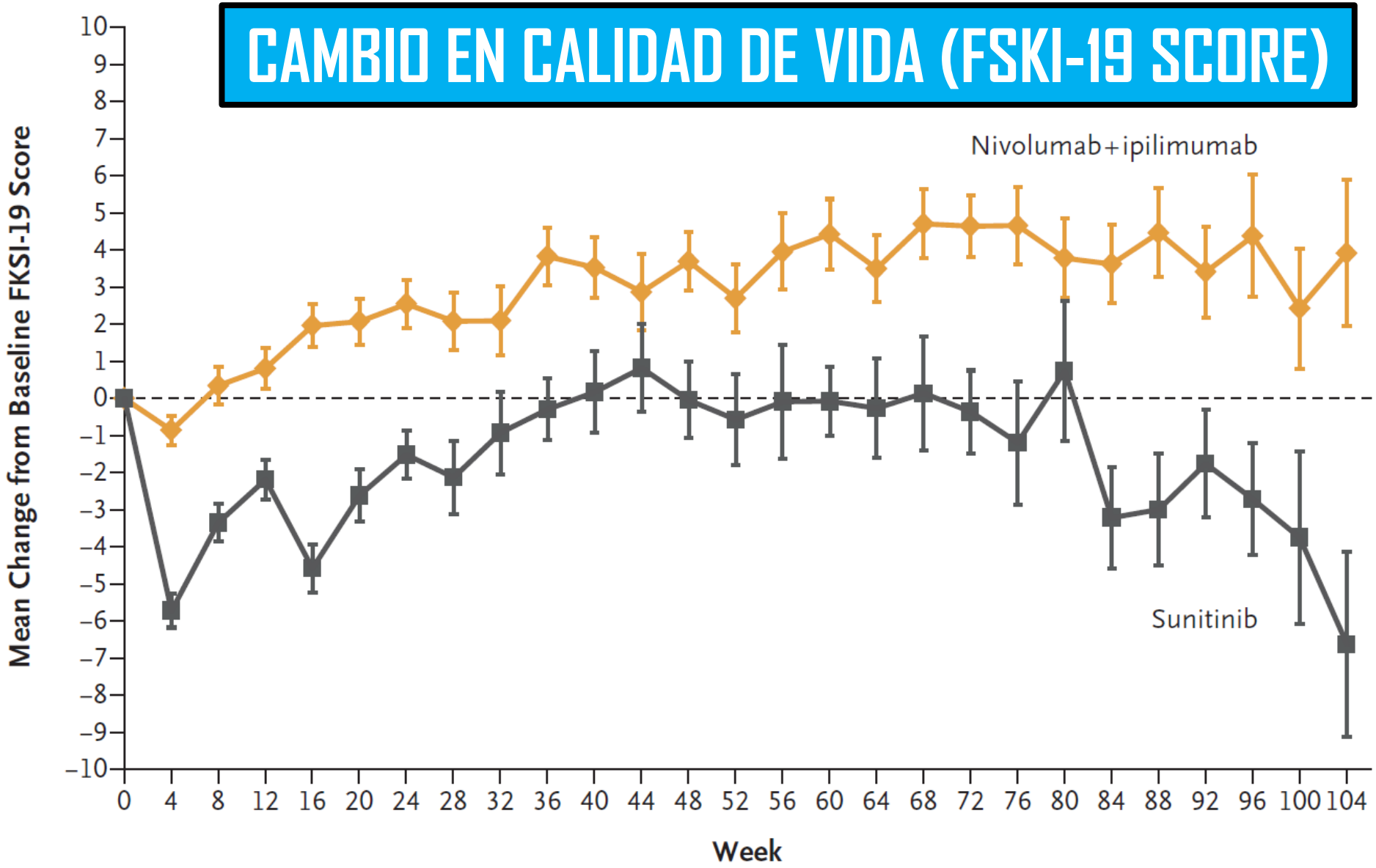
A 18 MESES: 75 Vs 60%

4-6 MESES DE SUPERVIVENCIA LIBRE DE PROGRESIÓN

Table 3. Treatment-Related Adverse Events Occurring in 15% or More of Treated Patients in Either Group.*

Event	Nivolumab plus Ipilimumab (N = 547)		Sunitinib (N = 535)	
	Any Grade†	Grade 3 or 4	Any Grade‡	Grade 3 or 4
	number of patients (percent)			
All events	509 (93)	250 (46)	521 (97)	335 (63)
Fatigue	202 (37)	23 (4)	264 (49)	49 (9)
Pruritus	154 (28)	3 (<1)	49 (9)	0
Diarrhea	145 (27)	21 (4)	278 (52)	28 (5)
Rash	118 (22)	8 (1)	67 (13)	0
Nausea	109 (20)	8 (1)	202 (38)	6 (1)
Increased lipase level	90 (16)	56 (10)	58 (11)	35 (7)
Hypothyroidism	85 (16)	2 (<1)	134 (25)	1 (<1)
Decreased appetite	75 (14)	7 (1)	133 (25)	5 (<1)
Asthenia	72 (13)	8 (1)	91 (17)	12 (2)
Vomiting	59 (11)	4 (<1)	110 (21)	10 (2)
Anemia	34 (6)	2 (<1)	83 (16)	24 (4)
Dysgeusia	31 (6)	0	179 (33)	1 (<1)
Stomatitis	23 (4)	0	149 (28)	14 (3)
Dyspepsia	15 (3)	0	96 (18)	0
Mucosal inflammation	13 (2)	0	152 (28)	14 (3)
Hypertension	12 (2)	4 (<1)	216 (40)	85 (16)
Palmar–plantar erythrodysesthesia	5 (<1)	0	231 (43)	49 (9)
Thrombocytopenia	2 (<1)	0	95 (18)	25 (5)

CAMBIO EN CALIDAD DE VIDA (FSKI-19 SCORE)



No. at Risk

Nivolumab+ipilimumab	425	347	281	239	212	180	166	152	143	139	125	108	76	44
Sunitinib	422	371	284	221	184	147	127	113	104	93	80	64	43	26

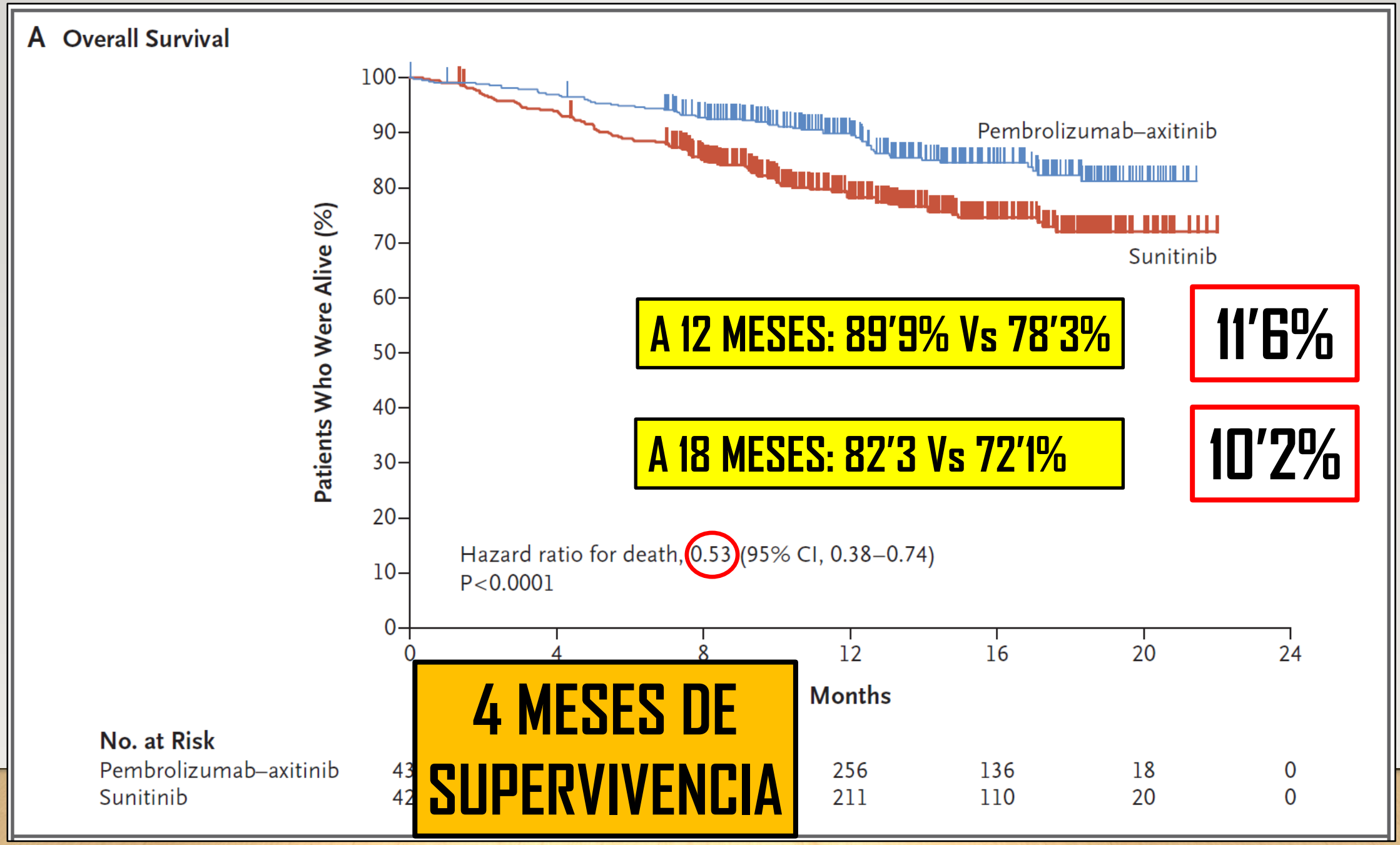
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

B.I. Rini, E.R. Plimack, V. Stus, R. Gafanov, R. Hawkins, D. Nosov, F. Pouliot, B. Alekseev, D. Soulières, B. Melichar, I. Vynnychenko, A. Kryzhanivska, I. Bondarenko, S.J[illegible]czylik, M. Markus, R.S. McDermott, J. Bedk[illegible]ada, Q. Shou, R.F. Perini, M. Chen, M.B. Atkins, and T. Powles, for the KEYNOTE-426 Investigators*

KEYNOTE-426


A Overall Survival
Patients Who Were Alive (%)
100
90
80
70
60
50
40
30
20
10
0
Pembrolizumab–axitinib
Sunitinib
A 12 MESES: 89'9% Vs 78'3%
11'6%
A 18 MESES: 82'3 Vs 72'1%
10'2%
Hazard ratio for death, 0.53 (95% CI, 0.38–0.74)
P<0.0001
0
4
8
12
16
20
24
Months
4 MESES DE SUPERVIVENCIA
No. at Risk
Pembrolizumab–axitinib 43 256 136 18 0
Sunitinib 42 211 110 20 0

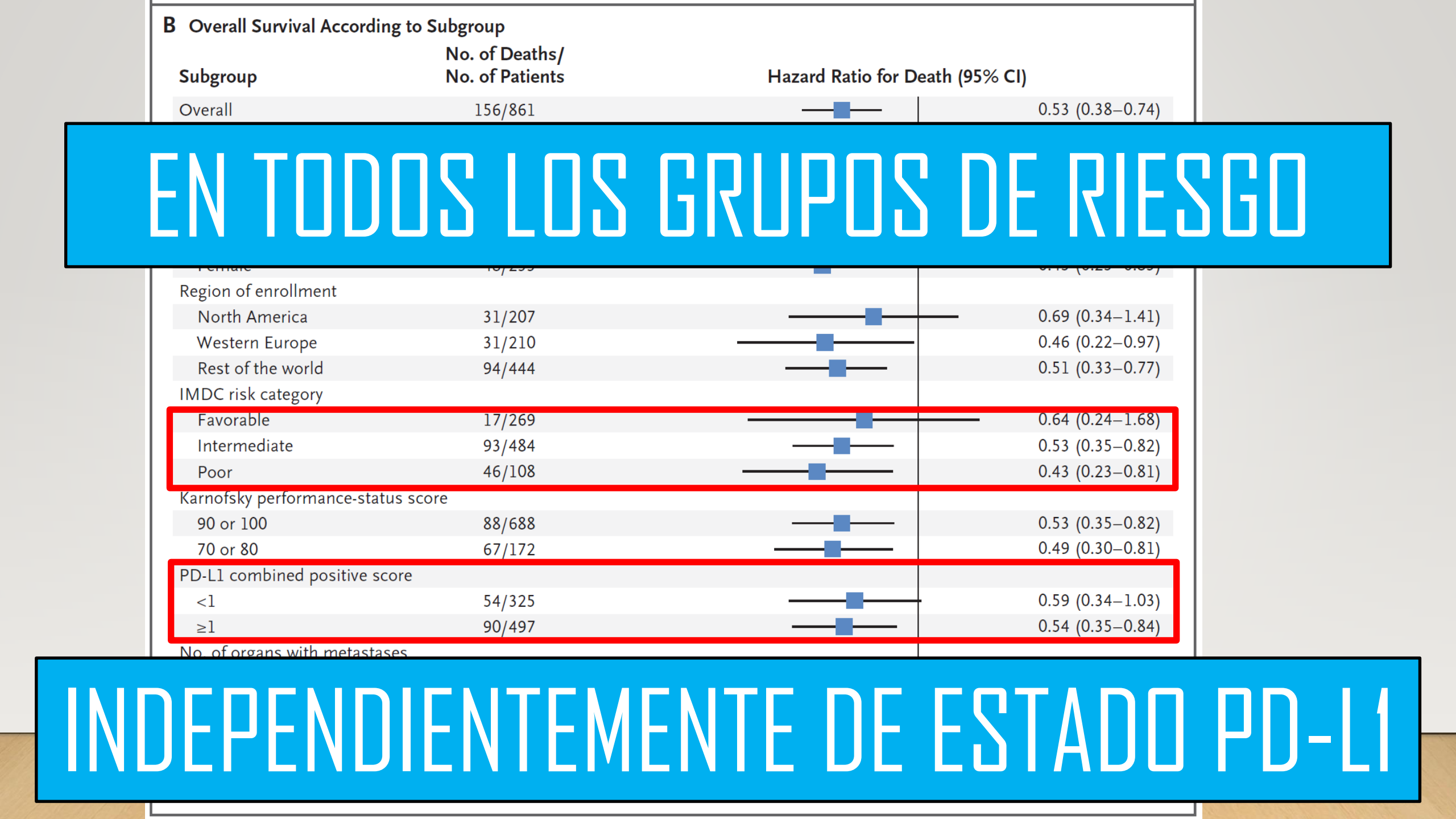
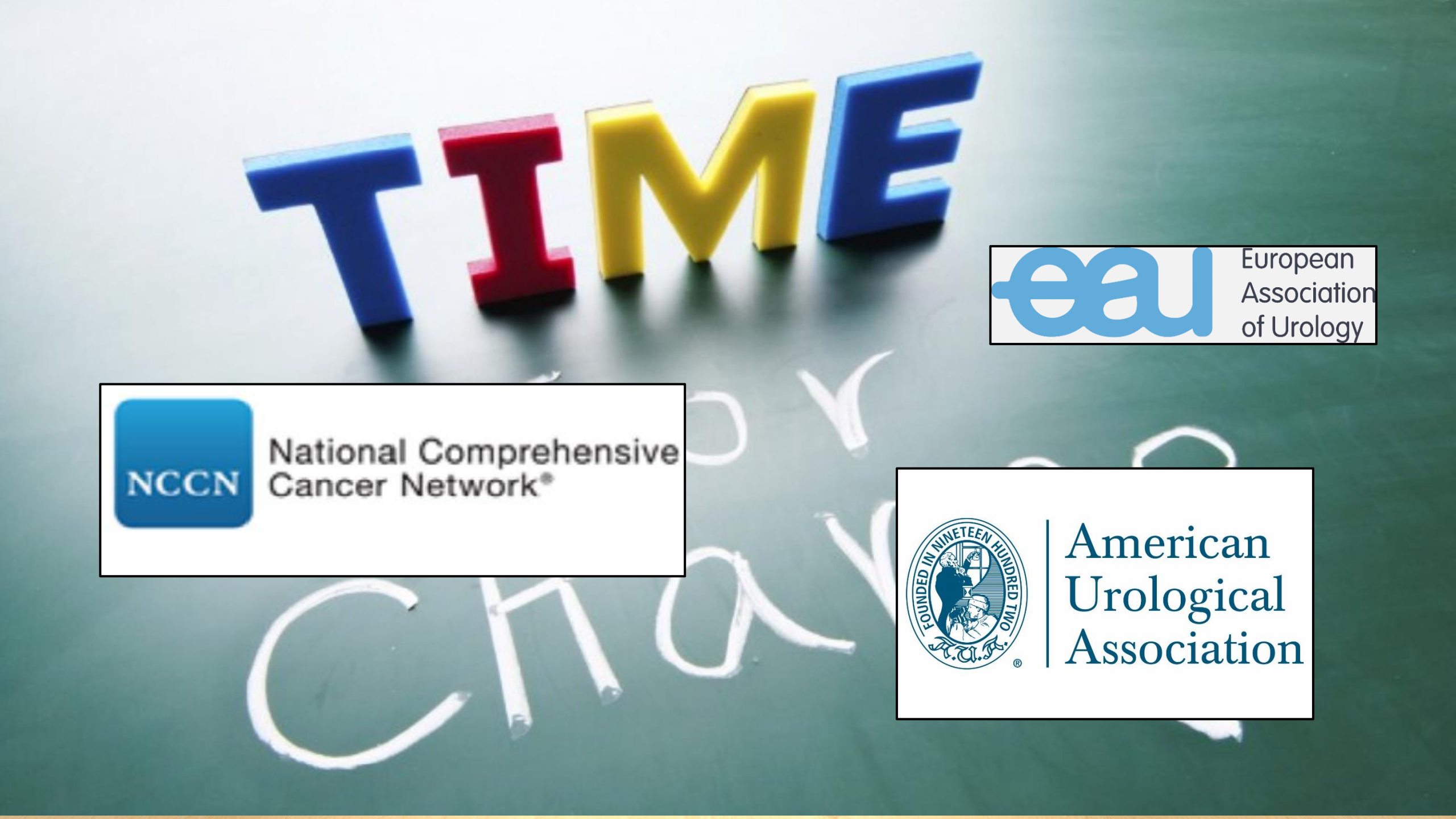

B Overall Survival According to Subgroup
Subgroup
No. of Deaths/ No. of Patients
Hazard Ratio for Death (95% CI)
Overall 156/861 0.53 (0.38–0.74)
EN TODOS LOS GRUPOS DE RIESGO
Region of enrollment
North America 31/207 0.69 (0.34–1.41)
Western Europe 31/210 0.46 (0.22–0.97)
Rest of the world 94/444 0.51 (0.33–0.77)
IMDC risk category
Favorable 17/269 0.64 (0.24–1.68)
Intermediate 93/484 0.53 (0.35–0.82)
Poor 46/108 0.43 (0.23–0.81)
Karnofsky performance-status score
90 or 100 88/688 0.53 (0.35–0.82)
70 or 80 67/172 0.49 (0.30–0.81)
PD-L1 combined positive score
<1 54/325 0.59 (0.34–1.03)
≥1 90/497 0.54 (0.35–0.84)
INDEPENDIENTEMENTE DE ESTADO PD-L1

Table 2. Summary of Confirmed Objective Response.*

Variable	Pembrolizumab–Axitinib (N = 432)	Sunitinib (N = 429)
Objective response rate — % (95% CI)†	59.3 (54.5 to 63.9)	35.7 (31.1 to 40.4)
Best overall response — no. (%)		
Complete response	25 (5.8)	8 (1.9)
Partial response	231 (53.5)	145 (33.8)
Stable disease	106 (24.5)	169 (39.4)
Progressive disease	47 (10.9)	73 (17.0)
Could not be evaluated‡	8 (1.9)	6 (1.4)
Not assessed§	15 (3.5)	28 (6.5)
Median time to response (range) — mo¶	2.8 (1.5 to 16.6)	2.9 (2.1 to 15.1)
Median duration of response (range) — mo‖	Not reached (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

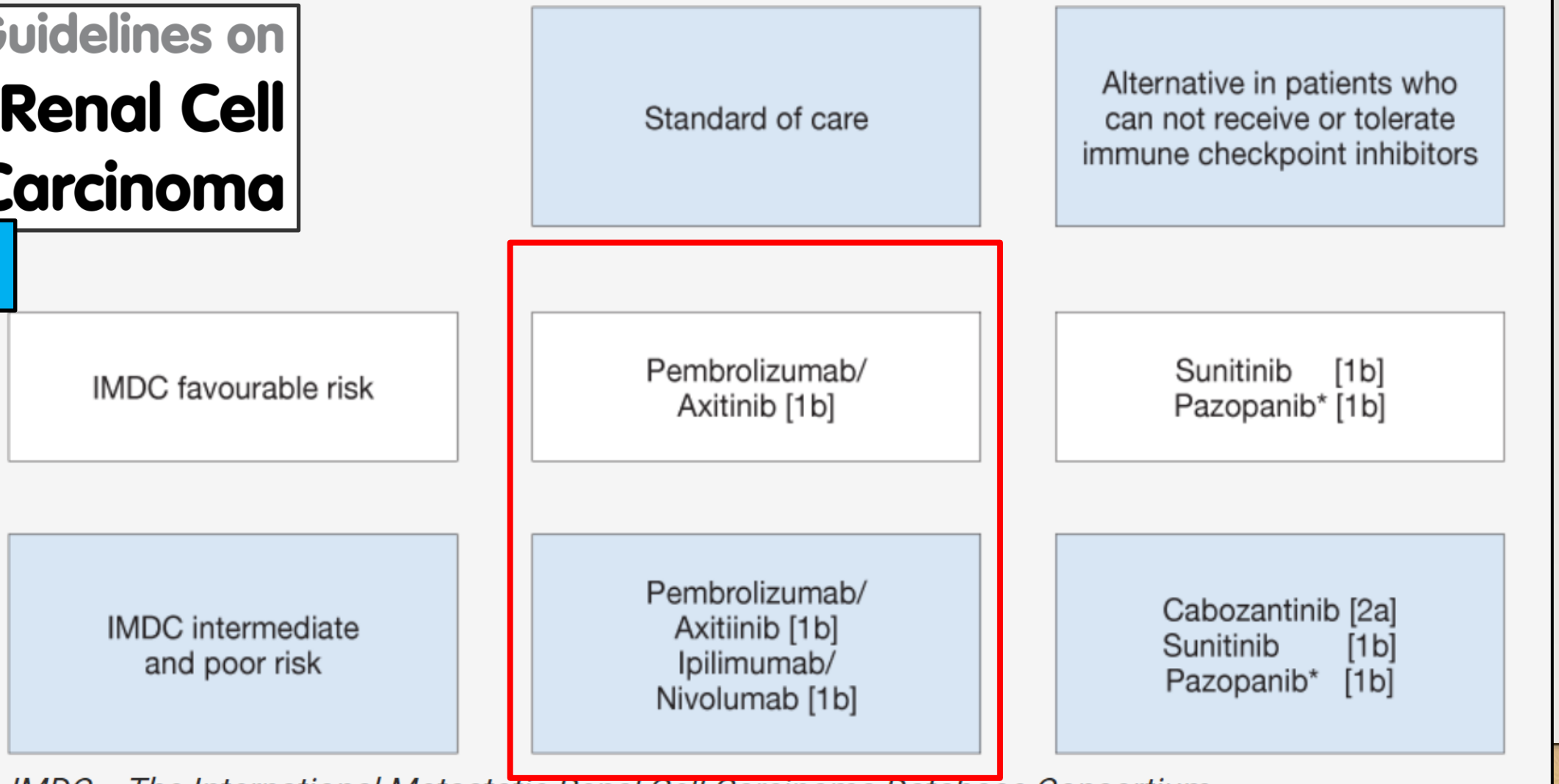

TIME
European Association of Urology
NCCN
National Comprehensive Cancer Network®
FOUNDED IN NINETEEN HUNDRED TWO
American Urological Association

EAU Guidelines on

Renal Cell Carcinoma

2020

Figure 7.1: Updated European Association of Urology Guidelines recommendations for the treatment of first-line and following lines in clear-cell metastatic renal cancer



IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Kidney Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred regimens	Other recommended regimens	Useful in certain circumstances
Favorable[a]	• Axitinib + pembrolizumab[b] • Pazopanib • Sunitinib	• Ipilimumab + nivolumab[b] • Axitinib + avelumab[b] • Cabozantinib (category 2B)	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d]
Poor/ intermediate[a]	• Ipilimumab + nivolumab[b] (category 1) • Axitinib + pembrolizumab[b] (category 1) • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab[b]	• Axitinib (category 2B) • High-dose IL-2[d] • Temsirolimus[e]

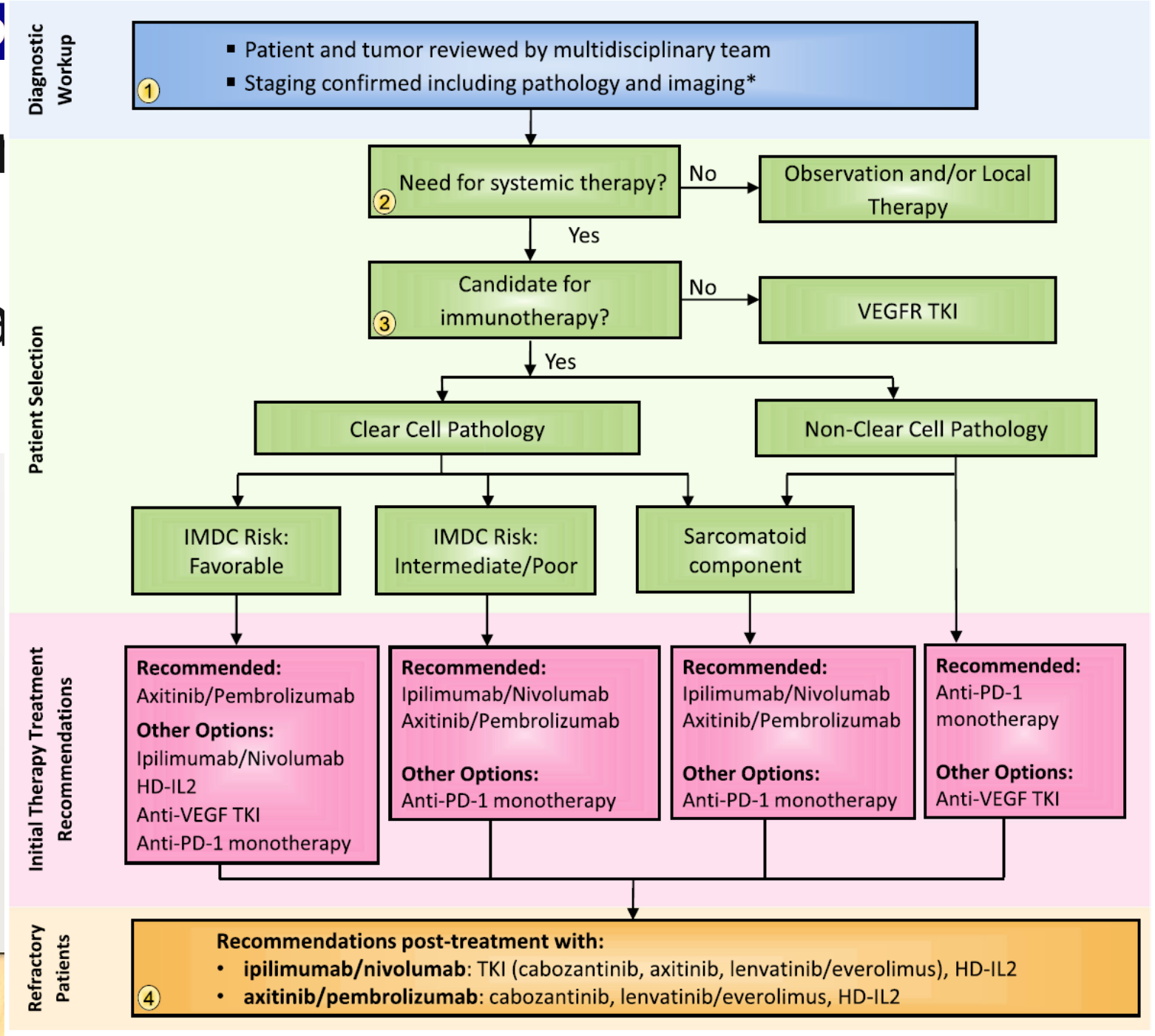
RELAPSE OR STAGE IV: SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY[n]

Preferred regimens	Other recommended regimens	Useful under certain circumstances
• Cabozantinib (category 1) • Nivolumab (category 1) • Ipilimumab + nivolumab	• Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Everolimus • Pazopanib • Sunitinib	• Bevacizumab (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients[l] (category 2B) • Temsirolimus (category 2B)[m]

POSITION ARTICLE AND GUID

The society for immu consensus statement for the treatment of a carcinoma (RCC)

Journal for ImmunoTherapy of Cancer



Evolución tto 1º Línea

CTLA-4

Ipilimumab + Nivolumab 4 cicles then Nivoluman (intermediate or poor risk) (Checkmate 214)

PD-1 and PD-L1 blockers

Pembrolizumab + Axitinib (KEYNOTE-426)

Avelumab + Axitinib (JAVELIN renal 101)

Atezolizumab +Bevacizumab (Immotion-151)

VEGF-targeted therapy

- Sunitinib
- Pazopanib
- Bevacizumab + INF α

Cabozantinib (intermediate or poor risk disease) (CABOSUN)

mTOR inhibitor

Temsirolimus (poor risk disease)

2006-2009 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022

Evolución tto 1º Línea

CTLA-4

Ipilimumab + Nivolumab 4 cicles then Nivoluman (intermediate or poor risk) (Checkmate 214)

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Pembrolizumab + Axitinib (KEYNOTE-426)

Avelumab + Axitinib (JAVELIN renal 101)

Atezolizumab +Bevacizumab (Immotion-151)

Nivolumab + Cabozantinib (CheckMate-9ER)

Pembrolizumab + Lenvantinib (CLEAR-arm2)

Pembrolizumab + Everolimus (CLEAR-arm1)

VEGF-targeted therapy

- Sunitinib
- Pazopanib
- Bevacizumab + INF α

Cabozantinib (intermediate or poor risk disease) (CABOSUN)

mTOR inhibitor

Temsirolimus (poor risk disease)

2006-2009 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022

Vs SUNITINIB

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 8, 2021 VOL. 384 NO. 14

Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma

R. Motzer, B. Alekseev, S.-Y. Rha, C… ünwald, T.E. Hutson, E. Kopyltsov, M.J. Méndez-Vidal, V. Kozlov, A. Alyasov… onso Gordoa, J.R. Merchan, E. Winquist, P. Maroto, J.C. Goh, M. Kim, H. Gurr… io, T. Takagi, B. Melichar, F. Rolland, U. De Giorgi, S. Wong, J. Bedke, M. S… Smith, L. Dutta, K. Mody, R.F. Perini, D. Xing, and T.K. Choueiri, for the CLEAR Trial Investigators*

CLEAR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma

T.K. Choueiri, T. Powles, M. Burotto, B. Escudier, M.T. Bourlon, B. Zurawski, V.M. C… amzaj, J.C. … rino, J. Żołn… hang, M…

CheckMate 9ER

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 8, 2021 VOL. 384 NO. 14

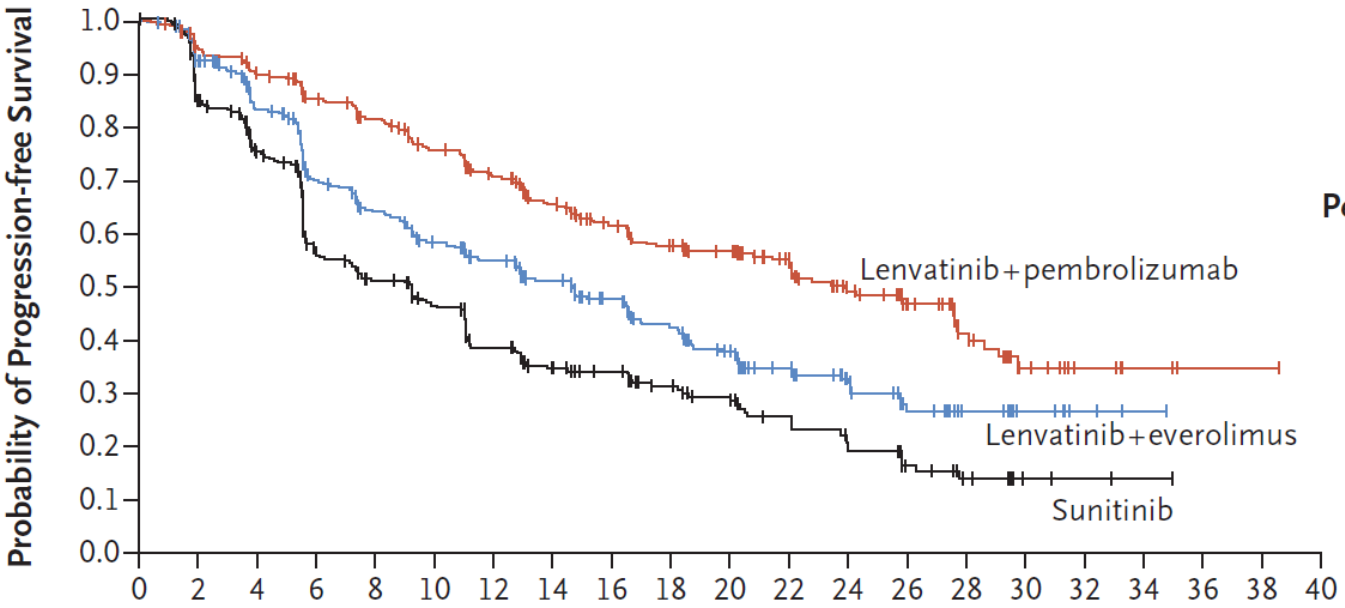
Lenvatinib plus Pembrolizumab or Everolimus

SLP (PFS)

CLEAR

Hr 0,39

A Kaplan–Meier Analysis of Progression-free Survival



	Median Progression-free Survival (95% CI) *mo*
Lenvatinib+ Pembrolizumab	23.9 (20.8–27.7)
Lenvatinib+ Everolimus	14.7 (11.1–16.7)
Sunitinib	9.2 (6.0–11.0)

Hazard ratio for disease progression or death (lenvatinib+ pembrolizumab vs. sunitinib), 0.39 (95% CI, 0.32–0.49); P<0.001

Hazard ratio for disease progression or death (lenvatinib+ ever…nitinib), …65 …–0.80); P<0…

No. at Risk

Lenvatinib+pembrolizumab	355	321	300	27	0
Lenvatinib+everolimus	357	305	259	20	
Sunitinib	357	262	218	14	

Lenvatinib + Pembrolizumab: 23.9 meses
Lenvatinib + Everolimus: 14.7 meses
Sunitinib: 9.2 meses

14.7

SLP (PFS)

The NEW ENGLAND

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ESTABLISH

Lenv

R. Motzer, B. Al
M.J. Méndez-Vidal, V
P. Maroto, J.C. Gc
U. De Giorgi, S. W

B Subgroup Analysis of Progression-free Survival

Subgroup	Lenvatinib+ Pembrolizumab	Sunitinib	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/no. of patients		
Overall	160/355	205/357	0.39 (0.32–0.49)
Rest of the world	74/157	97/158	0.36 (0.26–0.49)
MSKCC risk group			
Favorable	39/96	60/97	0.36 (0.23–0.54)
Intermediate	101/227	126/228	0.44 (0.34–0.58)
Poor	20/32	19/32	0.18 (0.08–0.42)
IMDC risk group			
Favorable	43/110	67/124	0.41 (0.28–0.62)
Intermediate	97/210	110/192	0.39 (0.29–0.52)
Poor	18/33	26/37	0.28 (0.13–0.60)
Baseline Karnofsky performance-status score			
100–90	125/295	172/294	0.38 (0.30–0.48)
80–70	35/60	33/62	0.44 (0.26–0.74)
No. of organs with metastases			
1	39/97	54/108	0.46 (0.30–0.71)
≥2	120/254	150/246	0.36 (0.28–0.47)
PD-L1 combined positive score			
≥1	51/107	78/119	0.40 (0.27–0.58)
<1	48/112	58/103	0.39 (0.26–0.59)

0.1 1.0 10.0

Lenvatinib+Pembrolizumab Better Sunitinib Better

En todos los grupos de riesgos IMDC
Independientemente estado PD-L1

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 8, 2021 VOL. 384 NO. 14

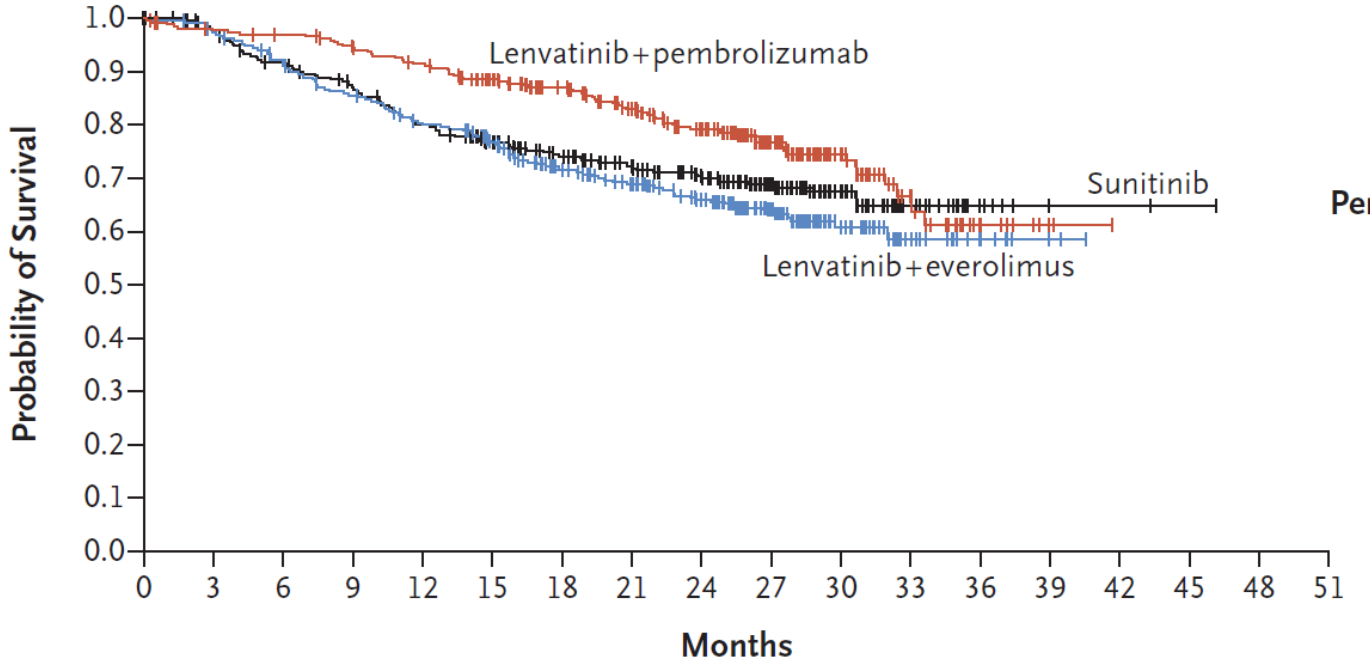
Lenvatinib plus Pembrolizumab or Everolimus

R.
M.J. Mé
P. M
U. D

SG (OS)

CLEAR

A Kaplan–Meier Analysis of Overall Survival



	Median Overall Survival (95% CI)
	mo
Lenvatinib+ Pembrolizumab	NR (33.6–NE)
Lenvatinib+ Everolimus	NR (NE–NE)
Sunitinib	NR (NE–NE)

Hazard ratio for death (lenvatinib+ pembrolizumab vs. sunitinib), 0.66 (95% CI, 0.49–0.88); P=0.005

Hazard ratio for death (lenvatinib+ ever
1.15
P=(

Hr 0,66

No. at Risk

Lenvatinib+pembrolizumab	355	342	338	327	313	280	253	222	188	129	66	26	10	2	0		
Lenvatinib+everolimus	357	346	321	299	277	246	205	183	154	109	46	22	8	2	0		
Sunitinib	357	332	307	289	264	236	207	186	160	112	60	25	7	2	2	1	0

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 8, 2021 VOL. 384 NO. 14

CLEAR

Ler

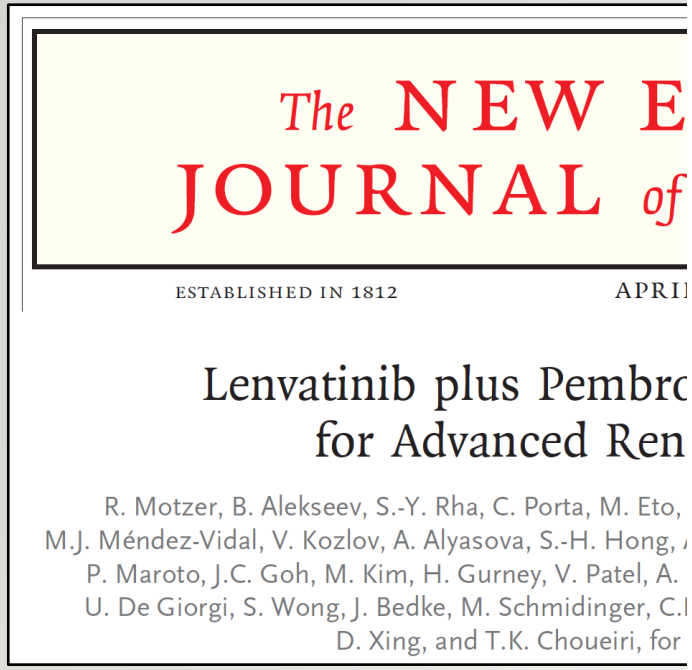
R. Motzer, B.
M.J. Méndez-Vidal
P. Maroto, J.C.
U. De Giorgi, S.

Table 2. Confirmed Tumor Responses.*

Measure	Lenvatinib plus Pembrolizumab (N=355)	Lenvatinib plus Everolimus (N=357)	Sunitinib (N=357)
Objective response (95% CI) — %†	71.0 (66.3–75.7)	53.5 (48.3–58.7)	36.1 (31.2–41.1)
Relative risk vs. sunitinib (95% CI)	1.97 (1.69–2.29)	1.48 (1.26–1.74)	Reference
Best overall response — no. (%)			
Complete response	57 (16.1)	35 (9.8)	15 (4.2)
Partial response	195 (54.9)	156 (43.7)	114 (31.9)
Stable disease	68 (19.2)	120 (33.6)	136 (38.1)
Pr			0)
U			8)
Media			16.62)
Media			16.7)

— mo

Tasa respuesta objetiva 71% con 16% respuesta completa



Event	Lenvatinib plus Pembrolizuma (N = 352)		Sunitinib (N = 340)	
	Any Grade	Grade ≥3†	Any Grade	Grade ≥3†
Any event	351 (99.7)	290 (82.4)	335 (98.5)	244 (71.8)
Diarrhea	216 (61.4)	34 (9.7)	168 (49.4)	18 (5.3)
Hypertension	195 (55.4)	97 (27.6)	141 (41.5)	64 (18.8)
Hypothyroidism‡	166 (47.2)	5 (1.4)	90 (26.5)	0
Decreased appetite	142 (40.3)	14 (4.0)	105 (30.9)	5 (1.5)
Fatigue	141 (40.1)	15 (4.3)	125 (36.8)	15 (4.4)
Nausea	126 (35.8)	9 (2.6)	113 (33.2)	2 (0.6)
Stomatitis	122 (34.7)	6 (1.7)	131 (38.5)	7 (2.1)
Dysphonia	105 (29.8)	0	14 (4.1)	0
Weight decrease	105 (29.8)	28 (8.0)	31 (9.1)	1 (0.3)
Proteinuria	104 (29.5)	27 (7.7)	43 (12.6)	10 (2.9)
Palmar–plantar erythrodysesthesia syndrome	101 (28.7)	14 (4.0)	127 (37.4)	13 (3.8)
Arthralgia	99 (28.1)	5 (1.4)	52 (15.3)	1 (0.3)
Rash	96 (27.3)	13 (3.7)	47 (13.8)	2 (0.6)
Vomiting	92 (26.1)	12 (3.4)	68 (20.0)	5 (1.5)
Constipation	89 (25.3)	3 (0.9)	64 (18.8)	0
Dysgeusia	43 (12.2)	1 (0.3)	95 (27.9)	1 (0.3)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma

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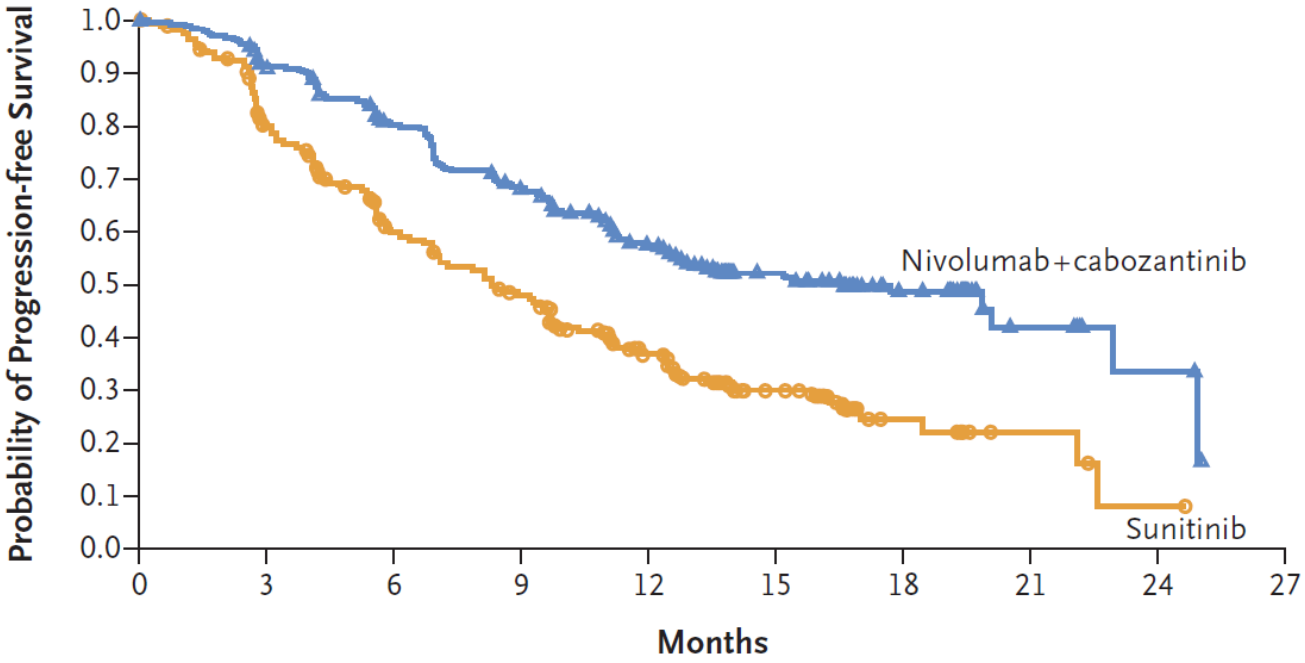
SLP (PFS)

A Progression-free Survival



	No. of Patients	Median (95% CI) *mo*
Nivolumab+ Cabozantinib	323	16.6 (12.5–24.9)
Sunitinib	328	8.3 (7.0–9.7)

Hazard ratio for disease progression or death, 0.51 (95% CI, 0.41–0.64)
P<0.001

No. at Risk														
Nivolumab+cabozantinib	323	279												0
Sunitinib	328	228												0

- Nivolumab + Cabozantinib: 16,6 meses
- Sunitinib: 8,3 meses

8,3

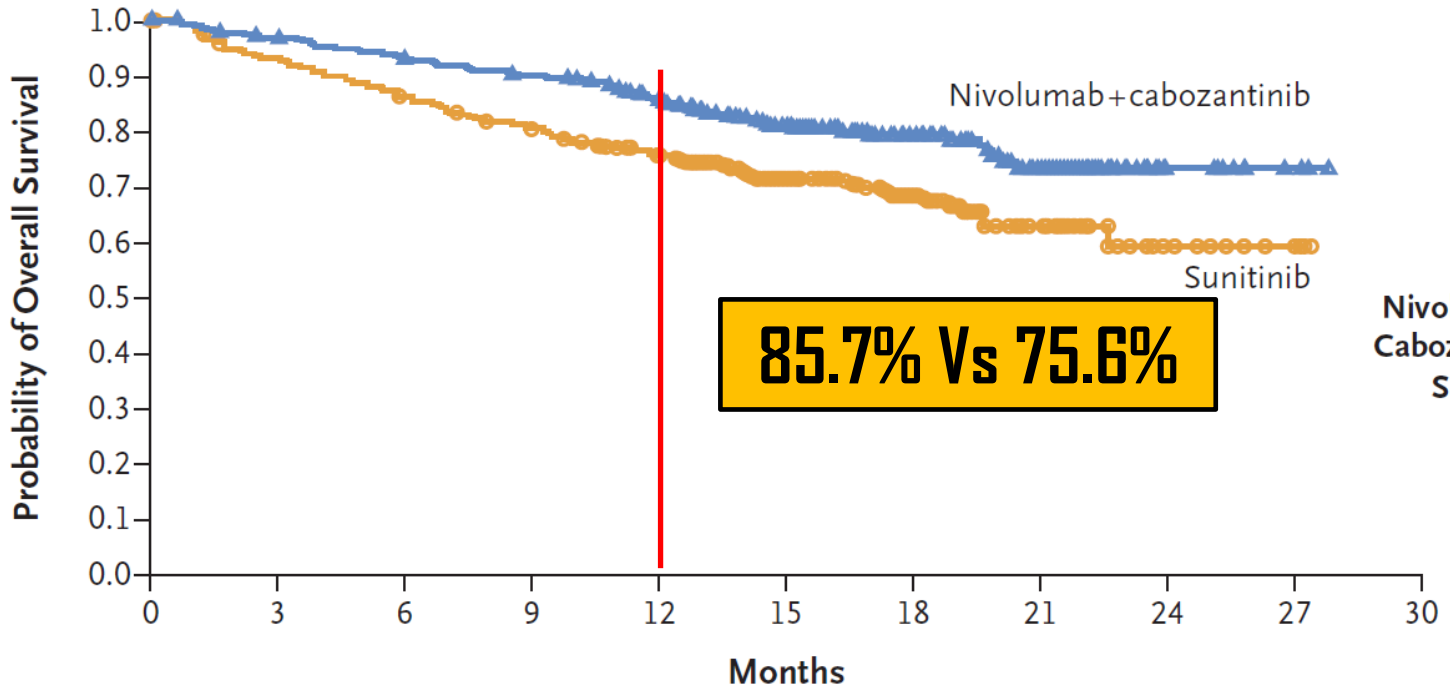
CheckMate 9ER

SG (OS)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

B Overall Survival



85.7% Vs 75.6%

	No. of Patients	Median (95% CI) *mo*
Nivolumab+ Cabozantinib	323	NR (NE)
Sunitinib	328	NR (22.6–NE)

Hazard ratio for death, 0.60 (98.89% CI, 0.40–0.89)
P=0.001

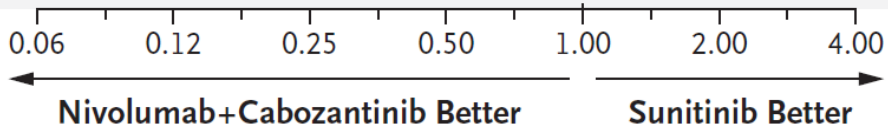
Hr 0,60

No. at Risk

Nivolumab+cabozantinib	323	308	295	283	259	184	106	55	11	3	0
Sunitinib	328	296	273	253	223	154	83	36	10	3	0

B Overall Survival, According to Subgroup

Subgroup	No. of Patients	Nivolumab+ Cabozantinib	Sunitinib	Hazard Ratio for Death (95% CI)
		no. of events/no. of patients		
Overall	651	67/323	99/328	0.60 (0.44–0.82)
Region				
United States and Europe	319	26/158	45/161	0.48 (0.30–0.79)
Rest of the world	332	41/165	54/167	0.71 (0.48–1.07)
IMDC prognostic risk				
Favorable	146	10/74	11/72	0.84 (0.35–1.97)
Intermediate	376	40/188	51/188	0.70 (0.46–1.07)
Poor	129	17/61	37/68	0.37 (0.21–0.66)
PD-L1 expression				
≥1%	166	28/83	30/83	0.80 (0.48–1.34)
<1% or indeterminate	485	39/240	69/245	0.51 (0.34–0.75)
Age				
<65 yr	401	31/191	66/210	0.44 (0.29–0.67)
≥65 yr	250	36/132	33/118	0.90 (0.56–1.44)
Sex				
Male				.40–0.85)
Female				.39–1.18)
Karnofsky performa				
90 or 100				.47–1.03)
70 or 80				.31–0.86)
Not reported				
Bone metastases				
Yes	150	24/78	33/72	0.54 (0.32–0.92)
No	501	43/245	66/256	0.61 (0.41–0.89)
Previous nephrectomy				
Yes	455	36/222	66/233	0.49 (0.33–0.74)
No	196	31/101	33/95	0.79 (0.48–1.29)



En todos los grupos de riesgos IMDC
Independientemente estado PD-L1

The NEW ENGLAND JOURNAL of MEDICINE

Niv
Sunitini

T.K. Chouei
V.M. Oyervi
J.C. Goh,
J. Żołnierek
M.A.

CheckMate 9ER

Table 3. Adverse Events (As-Treated Population).*

Event	Nivolumab plus Cabozantinib (N = 320)		Sunitinib (N = 320)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any event	319 (99.7)	241 (75.3)	317 (99.1)	226 (70.6)
Diarrhea	204 (63.8)	22 (6.9)	151 (47.2)	14 (4.4)
Palmar–plantar erythrodysesthesia	128 (40.0)	24 (7.5)	130 (40.6)	24 (7.5)
Hypertension	111 (34.7)	40 (12.5)	119 (37.2)	42 (13.1)
Hypothyroidism	109 (34.1)	1 (0.3)	94 (29.4)	1 (0.3)
Fatigue	103 (32.2)	11 (3.4)	111 (34.7)	15 (4.7)
Increased ALT level	90 (28.1)	17 (5.3)	27 (8.4)	7 (2.2)
Decreased appetite	90 (28.1)	6 (1.9)	65 (20.3)	4 (1.2)
Nausea	85 (26.6)	2 (0.6)	98 (30.6)	1 (0.3)
Increased AST level	81 (25.3)	11 (3.4)	35 (10.9)	4 (1.2)
Dysgeusia	76 (23.8)	0	69 (21.6)	0
Asthenia	71 (22.2)	14 (4.4)	59 (18.4)	10 (3.1)
Rash	69 (21.6)	6 (1.9)	26 (8.1)	0
Mucosal inflammation	66 (20.6)	3 (0.9)	81 (25.3)	8 (2.5)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

CheckMate 9ER

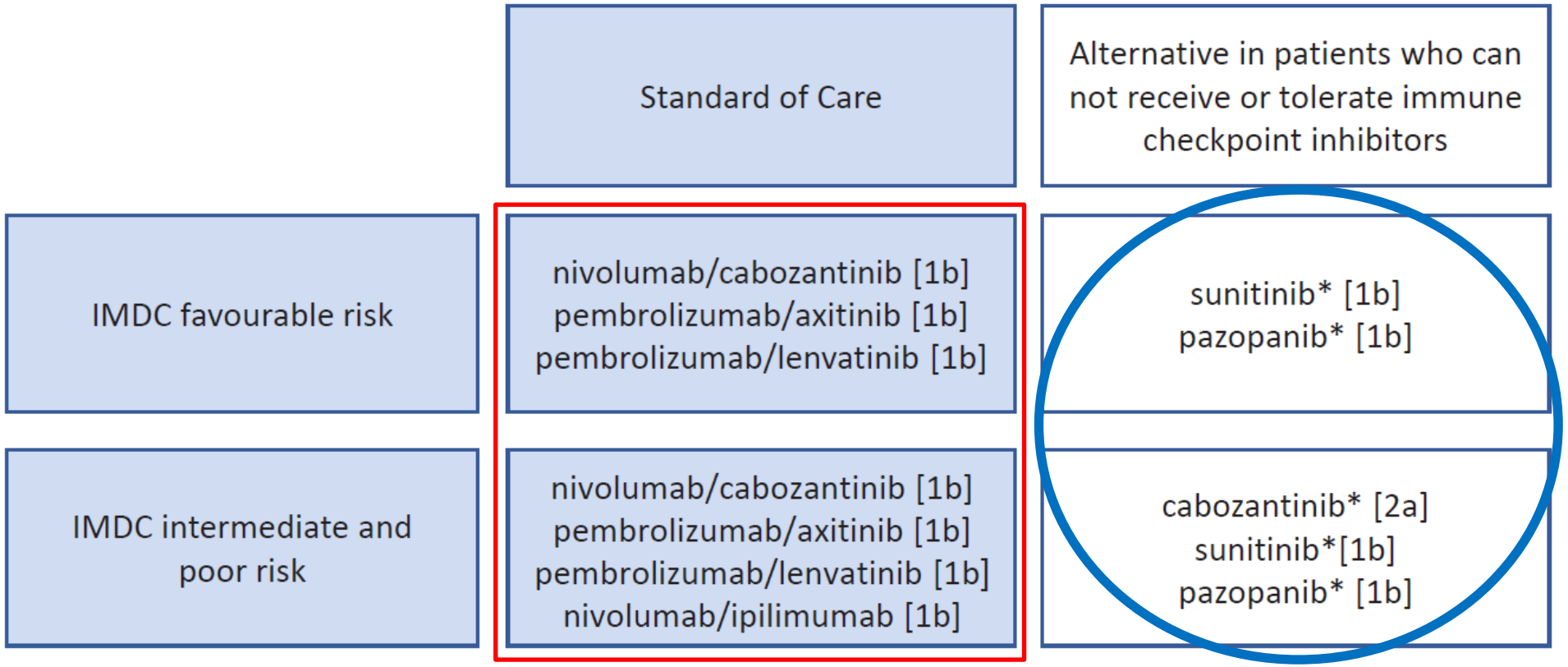
Table 2. Objective Response (Intention-to-Treat Population).*

Variable	Nivolumab plus Cabozantinib (N = 323)	Sunitinib (N = 328)
Confirmed objective response — % (95% CI)†	55.7 (50.1–61.2)	27.1 (22.4–32.3)
Confirmed best overall response — no. (%)		
Complete response	26 (8.0)	15 (4.6)
Partial response	154 (47.7)	74 (22.6)
Stable disease	104 (32.2)	138 (42.1)
Progressive		3.7)
Unable to d		7.1)
Median time to		–6.9)
Median duratio		–18.4)

Tasa de respuesta objetiva de 55.7% con un 8% de respuesta completa


TODAS LAS PRIMERAS OPCIONES SON COMBOS
TODAS LAS OPCIONES VAN CON INMUNOTERAPIA

Figure 7.1: Updated EAU Guidelines recommendations for the first-line treatment of metastatic clear-cell RCC



IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium
**pazopanib for intermediate-risk disease only.*
[1b] = based on one randomised controlled phase III trial.
[2a] = based on a well-designed study without randomisation, or a subgroup analysis of a randomised controlled trial.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Kidney Cancer

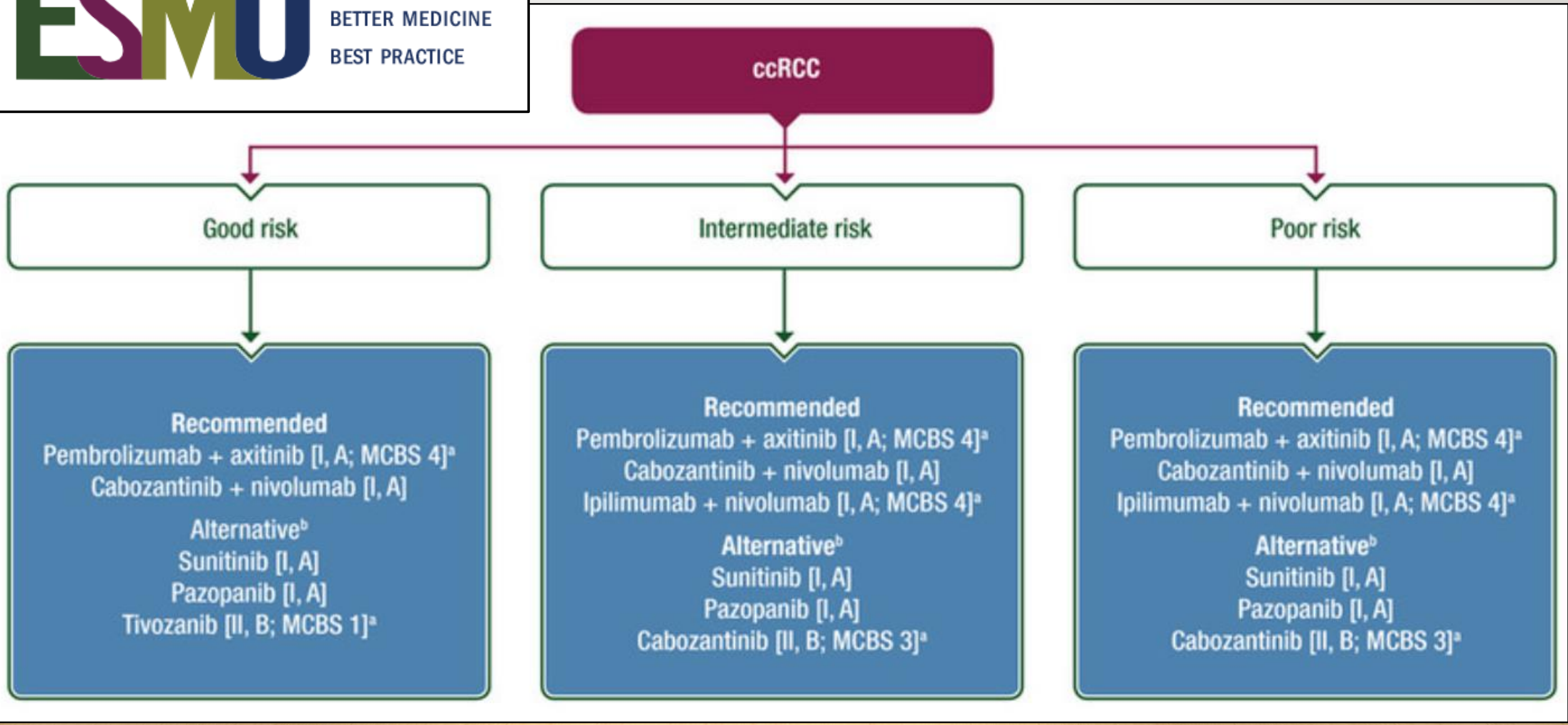
NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1)	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Ipilimumab + nivolumab[b] • Pazopanib • Sunitinib	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d] (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Ipilimumab + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B) • High-dose IL-2[d] (category 3) • Temsirolimus[e] (category 3)

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE



TRATAMIENTO SISTÉMICO EN PRIMERA LÍNEA

¿Mono Vs Combo?

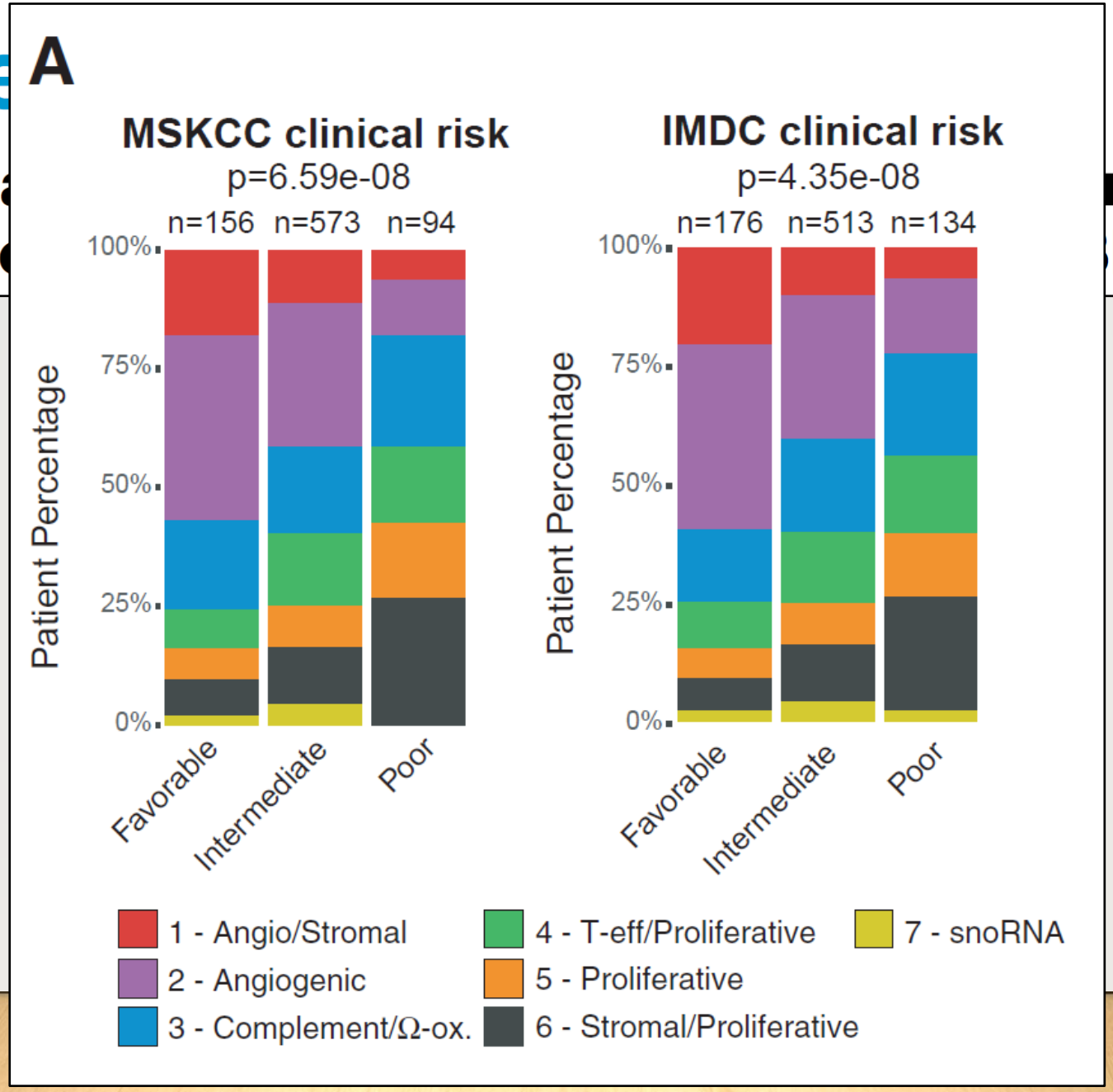
¿GRUPO PX FAVORABLE?

¿Modelo IMDC, sirve pero… Es fiable?

Cance

Molecula ne

Outcome lockade



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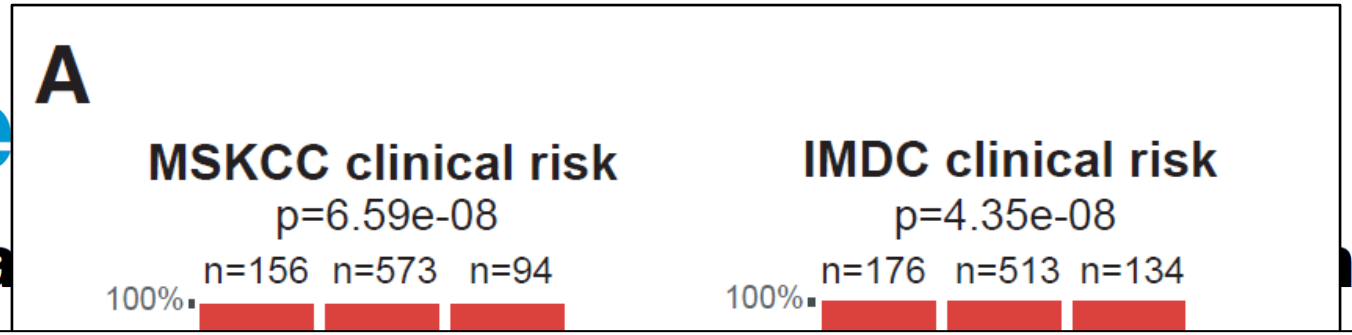
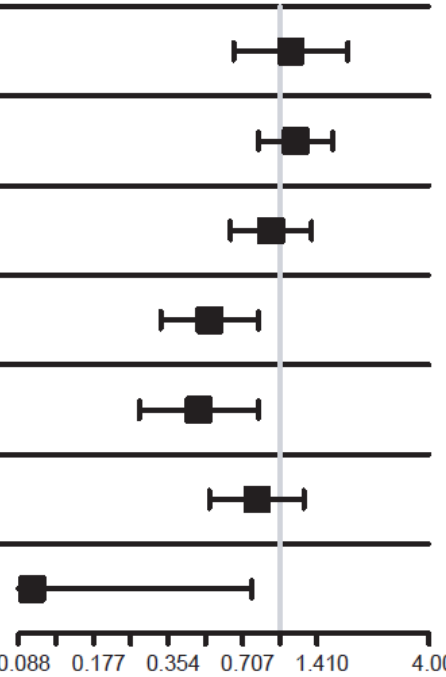


D

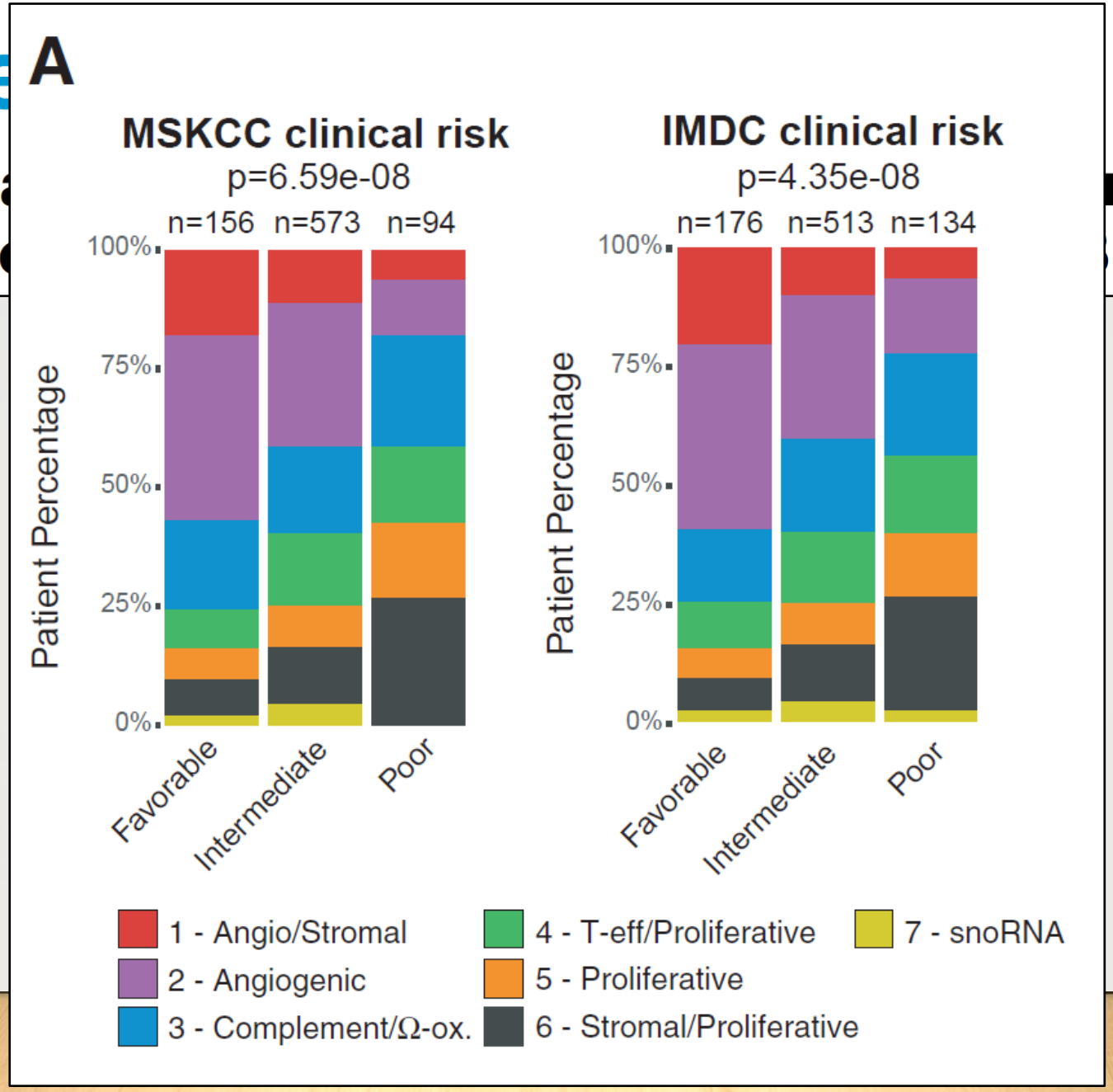
Cluster	PFS HR (95% CI)	p-value	A/B mPFS	Sunitinib mPFS
1 - Angio/stromal	1.11 (0.65−1.88)	0.708	15.3	13.9
2 - Angiogenic	1.16 (0.82−1.63)	0.397	13.8	14.2
3 - Complement/Ω-ox.	0.92 (0.63−1.34)	0.666	8.1	7.1
4 - T-eff/Proliferative	0.52 (0.33−0.82)	0.005	10.9	6.1
5 - Proliferative	0.47 (0.27−0.82)	0.007	8.3	4.3
6 - Stromal/Proliferative	0.81 (0.52−1.25)	0.331	6.8	5.2
7 - snoRNA	0.10 (0.01−0.77)	0.028	NR	7.4



Cance

Molecula ne

Outcome lockade



TRATAMIENTO SISTÉMICO EN PRIMERA LÍNEA

¿Mono Vs Combo?

¿GRUPO PX FAVORABLE?

¿Modelo IMDC, sirve pero… Es fiable?

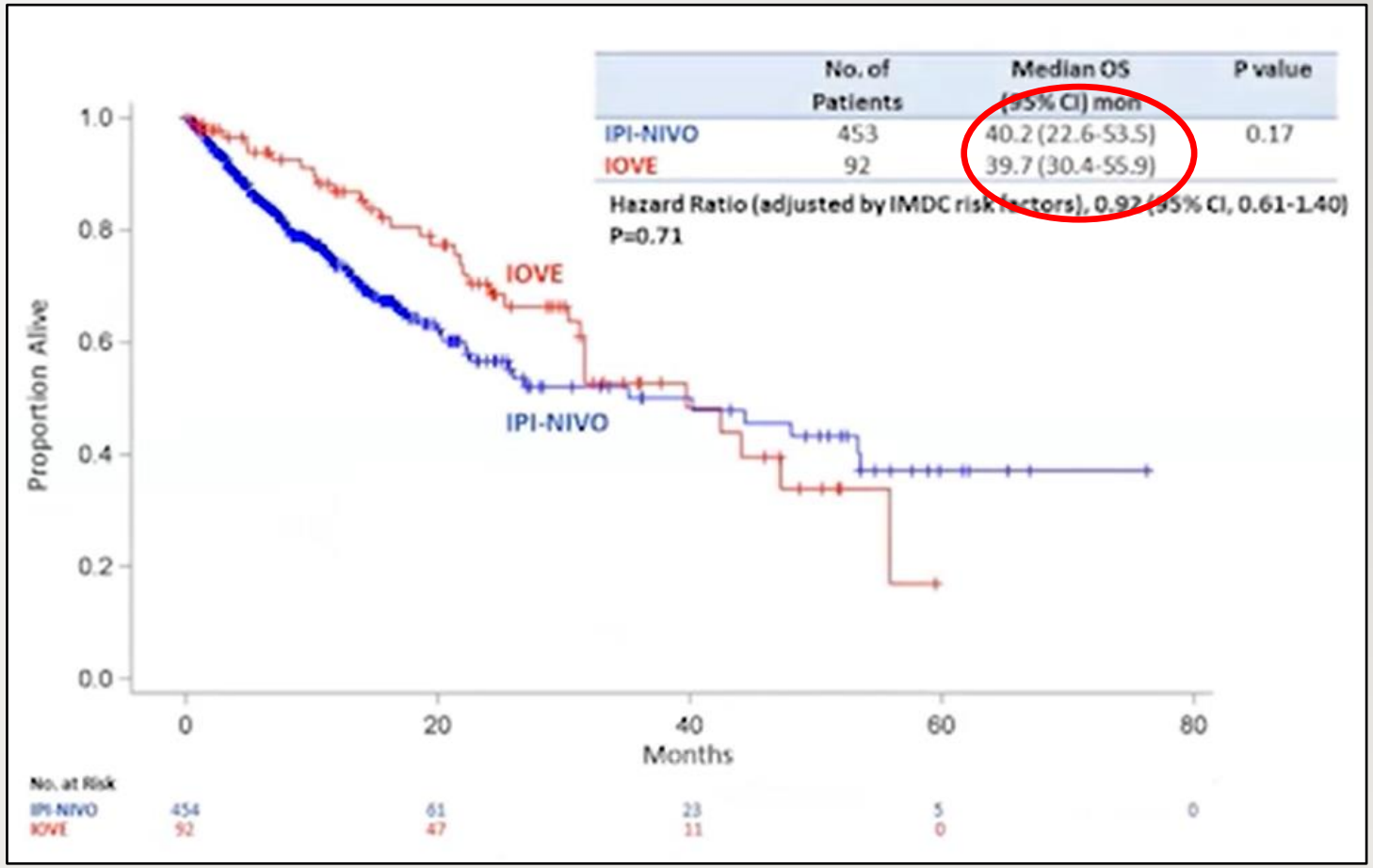
IOIO Vs IOTKI

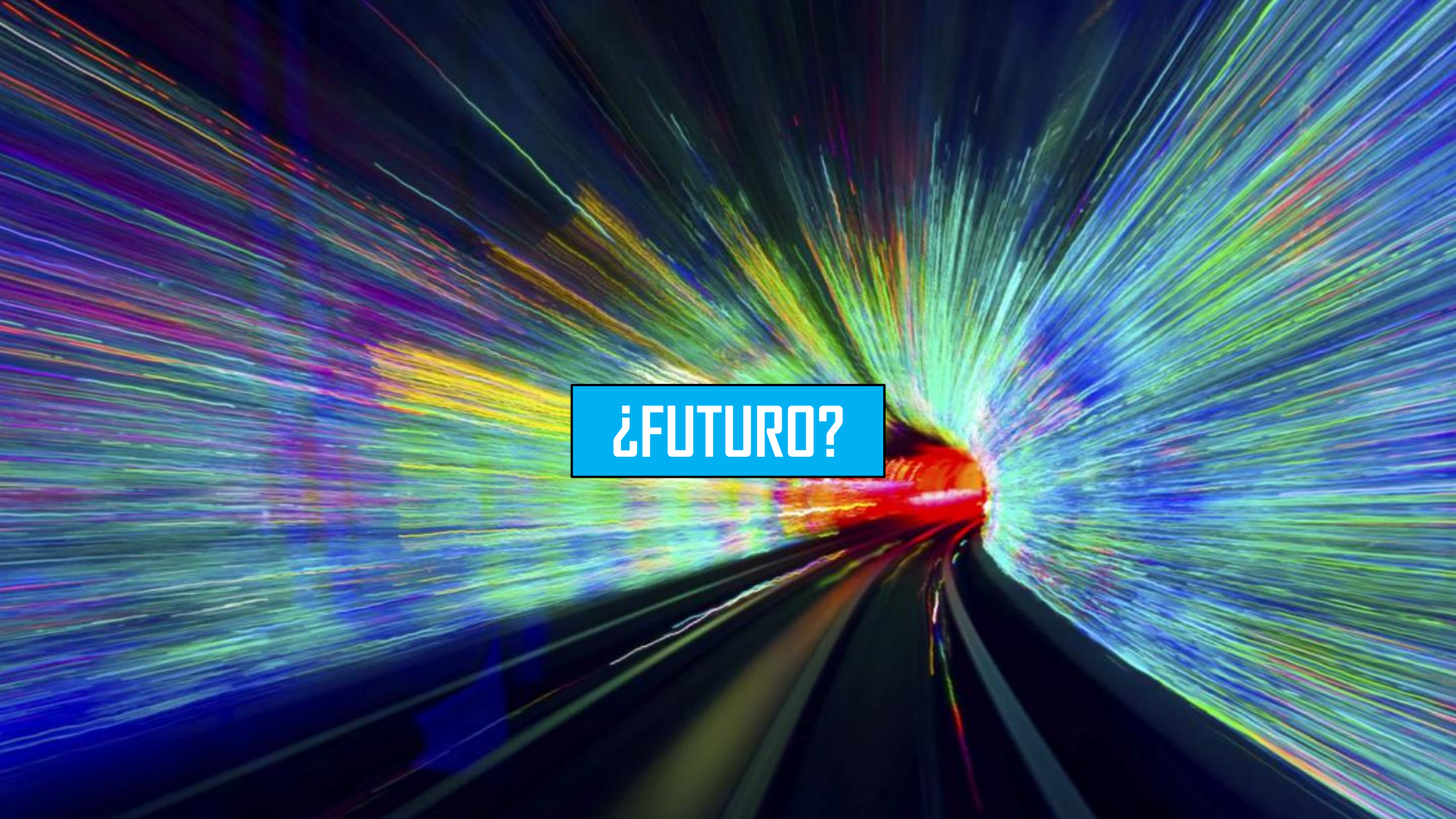
2021 ASCO® ANNUAL MEETING

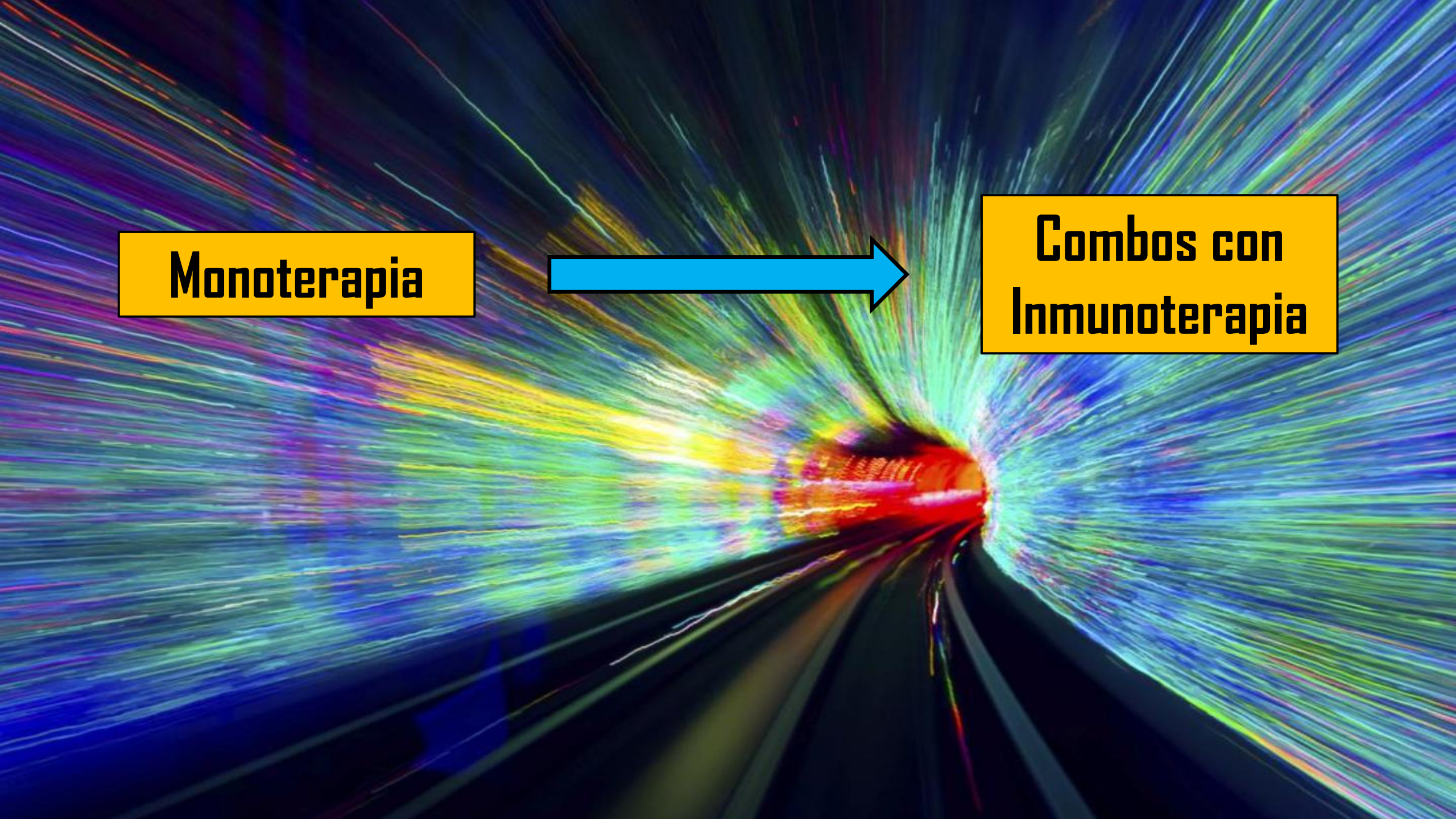
#ASCO21

No hay diferencias en supervivencia global

Datos retrospectivos




¿FUTURO?


Monoterapia
Combos con Inmunoterapia

Evolución tto 1º Línea

CTLA-4

PD-1 and PD-L1 blockers

VEGF-targeted therapy

- Sunitinib
- Pazopanib
- Bevacizumab + INF α

mTOR inhibitor

Temsirolimus (riesgo pobre)

2006-2009

2017

Cabozantinib (riesgo intermedio o pobre) (CABOSUN)

2018

Ipilimumab + Nivolumab 4 cicles then Nivoluman (riesgo intermedio o pobre) (Checkmate 214)

2019

Pembrolizumab + Axitinib (KEYNOTE-426)

Avelumab + Axitinib (JAVELIN renal 101)

Atezolizumab +Bevacizumab (Immotion-151)

2020

Nivolumab + Cabozantinib (CheckMate-9ER)

Pembrolizumab + Lenvantinib (CLEAR-arm2)

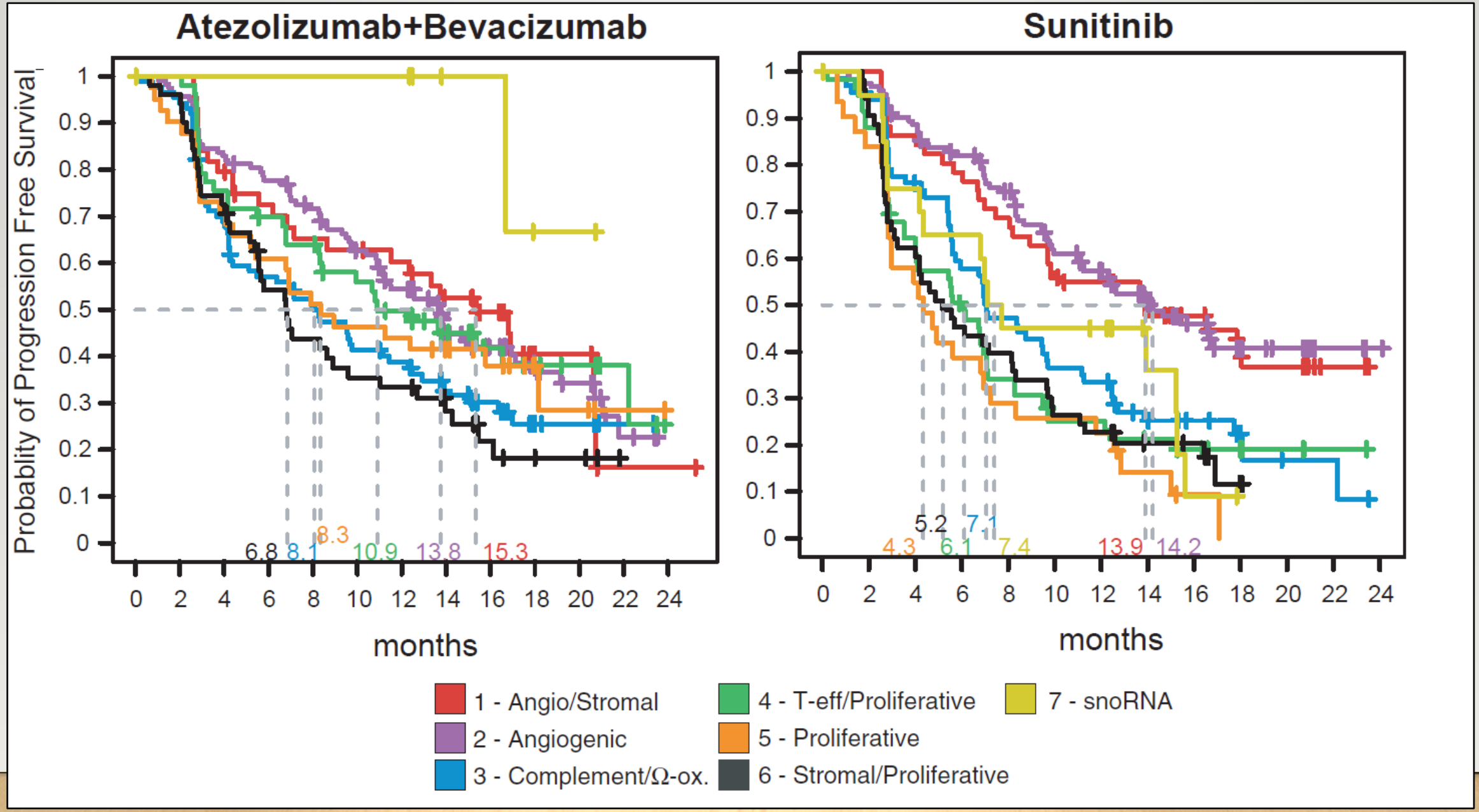
Pembrolizumab + Everolimus (CLEAR-arm1)

2021

Ipilimumab + Nivolumab + Cabozantinib 4 ciclos, luego Nivolumab + Cabozantinib (riesgo intermedio o pobre) (COSMIC-313)

Ipilimumab + Nivolumab 4 ciclos luego Nivolumab + Cabozantinib) (PDIGREE)

2022


Atezolizumab+Bevacizumab
Sunitinib
Probablity of Progression Free Survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 2 4 6 8 10 12 14 16 18 20 22 24
months
6.8
8.1
8.3
10.9
13.8
15.3
5.2
4.3
6.1
7.1
7.4
13.9
14.2
1 - Angio/Stromal
2 - Angiogenic
3 - Complement/Ω-ox.
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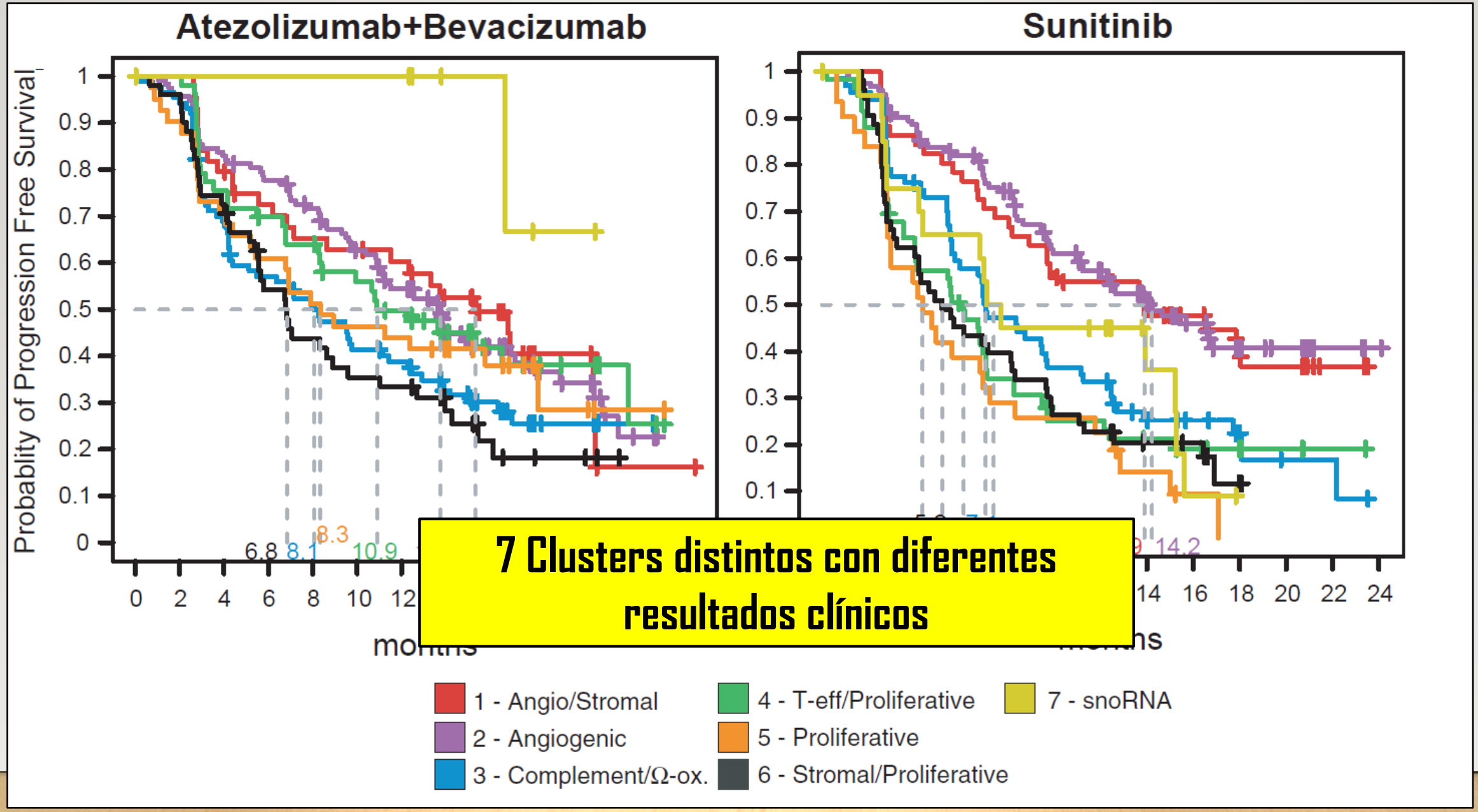
5 - Proliferative
6 - Stromal/Proliferative
7 - snoRNA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Probablity of Progression Free Survival
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0.5
0.4
0.3
0.2
0.1
0
0 2 4 6 8 10 12
14 16 18 20 22 24
6.8
8.1
8.3
10.9
14.2
months
7 Clusters distintos con diferentes resultados clínicos
1 - Angio/Stromal
2 - Angiogenic
3 - Complement/Ω-ox.
4 - T-eff/Proliferative
5 - Proliferative
6 - Stromal/Proliferative
7 - snoRNA


SELECCIÓN DE PACIENTES

CONCLUSIONES

1. El CCR es un tumor urológico frecuente con un porcentaje alto de MTX al inicio o bien durante el seguimiento.
2. El entendimiento de la Biología Molecular del CCR nos ha permitido mejorar las dianas terapéuticas y aumentar la supervivencia.
3. El tratamiento con combos con inmunoterapia está revolucionando el tratamiento con beneficio claro sobre la SG del paciente.
4. El futuro de las posibles combinaciones es prometedor, estamos a la espera de sus resultados.


Muchas gracias