Metastatic kidney cancer – novel treatment approaches

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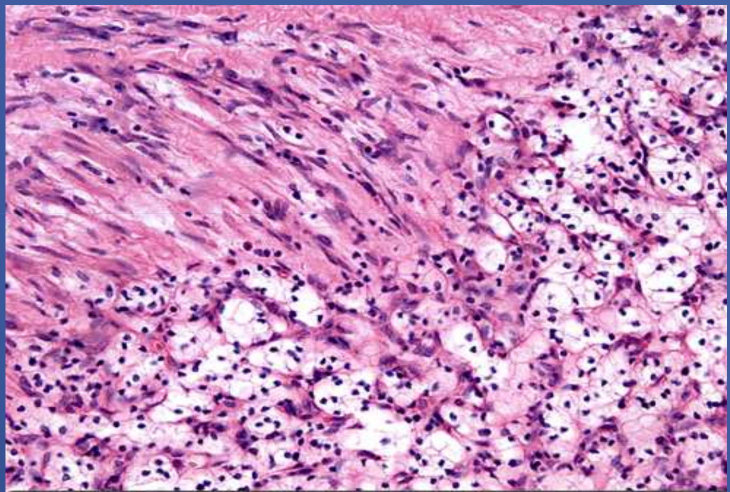
Contemporary Oncology Symposium Poznan 15-17.2019

Renal cell carcinoma RCC epidemiology



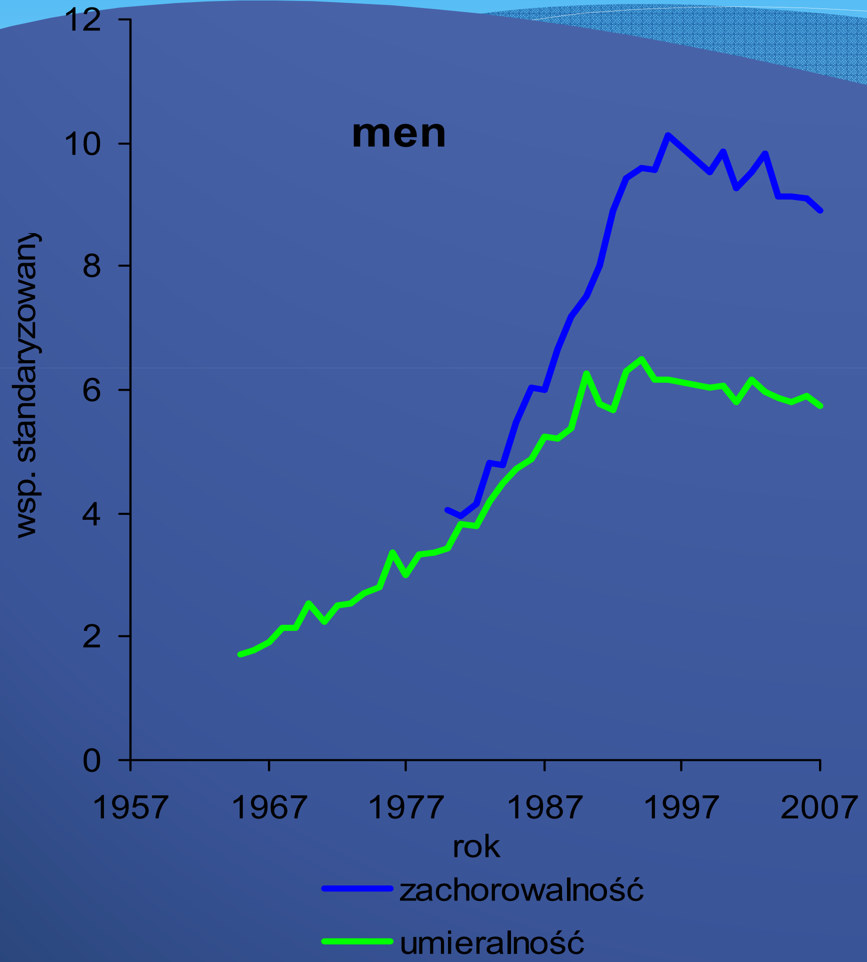
RCC x20[1]

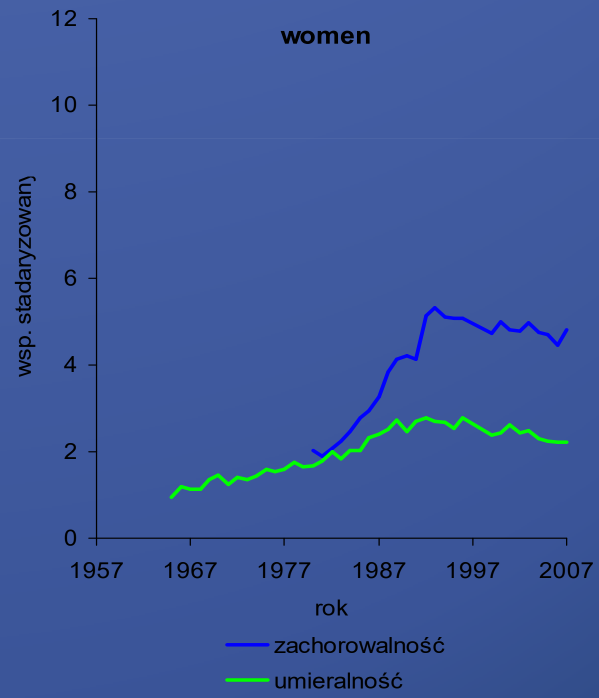
* RCC **3%** of all adult tumors and **90–95%** kidney tumors
* frequency : 3/10 000

(in Poland 5200 /rok/38 000 000 inhabitants)

* M/F ratio : 1.6/1
* Medium age**~ 60 yrs**

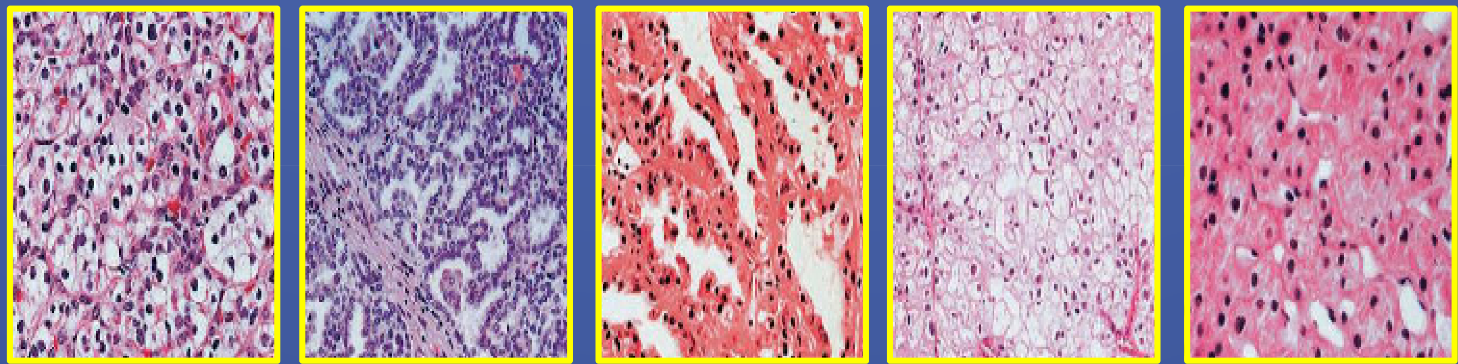
RCC morbidity and mortality trends in Poland 1965-2007





RCC Subtypes

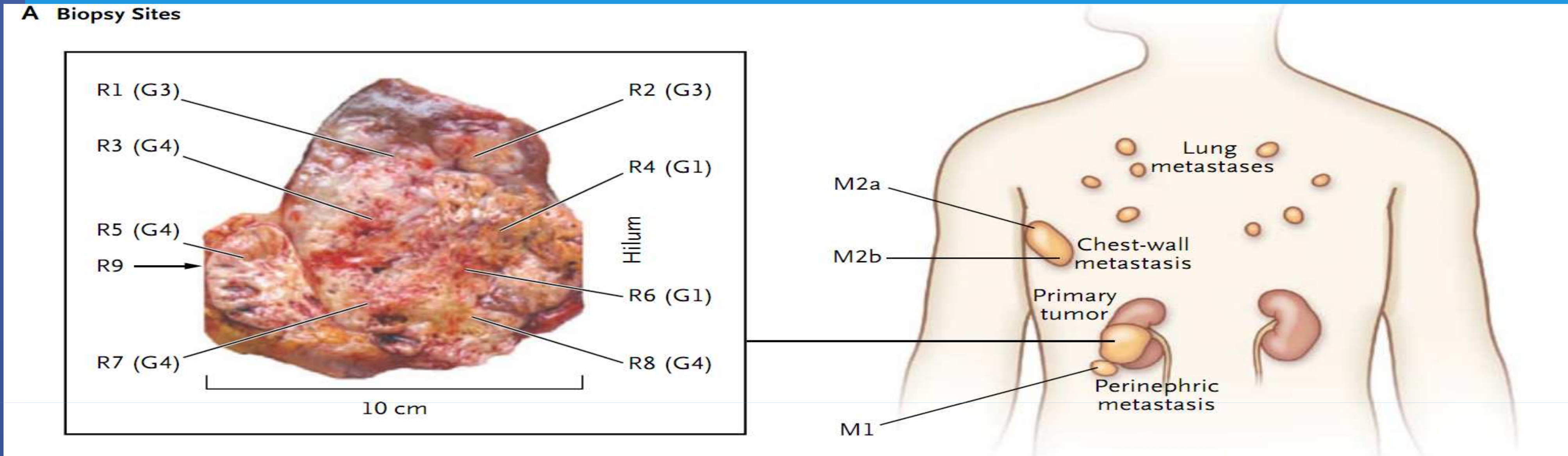
* RCC is a heterogeneous group of diseases
* Different neoplasms characterized by distinct histologies, natural histories, and responses to therapy

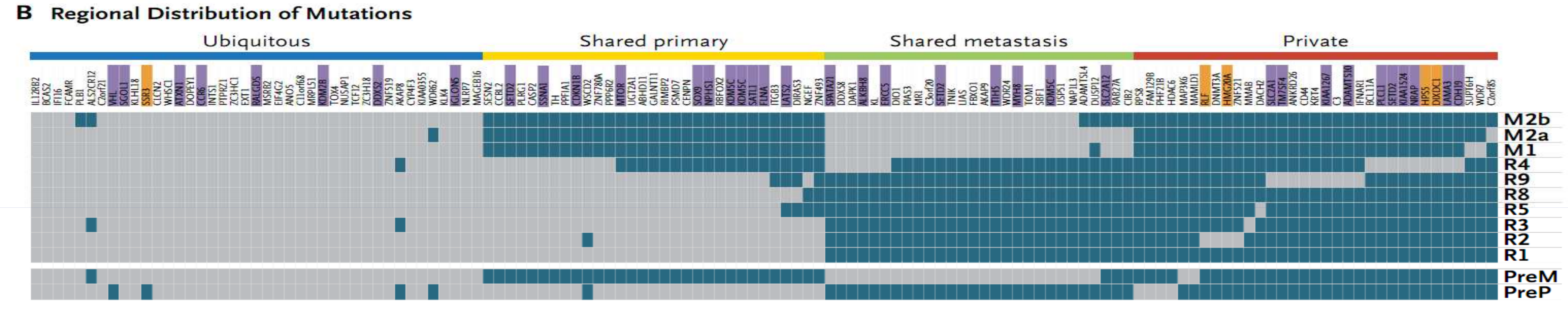


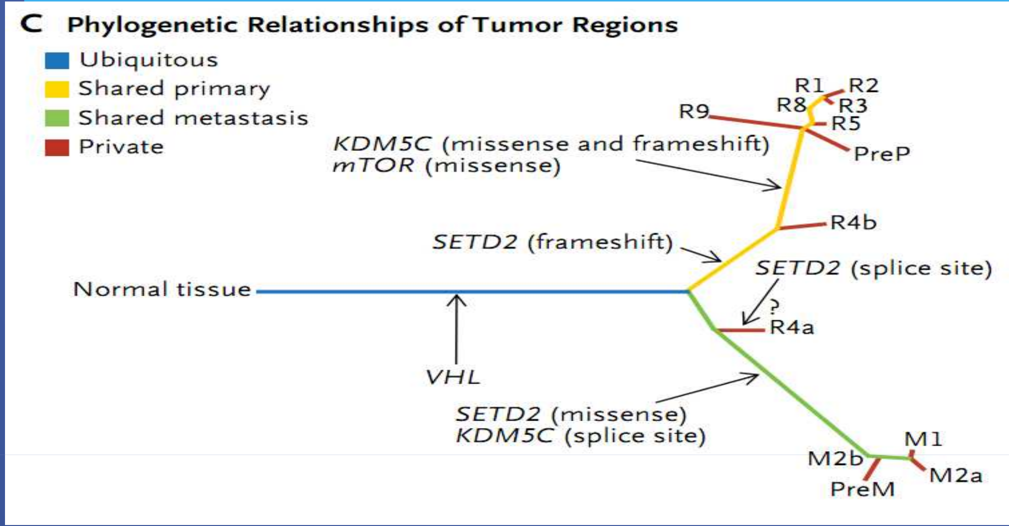
Clear cell	Papillary type 1	Papillary type 2	Chromophobe	Oncocytoma
75%	*5%*	*10%*	*5%*	*5%*

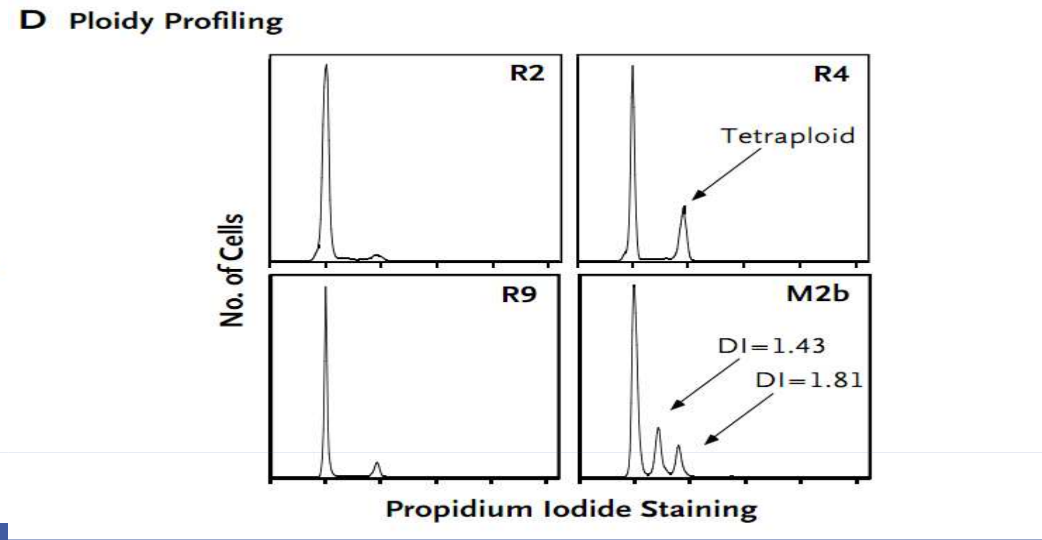
Incidence (%)

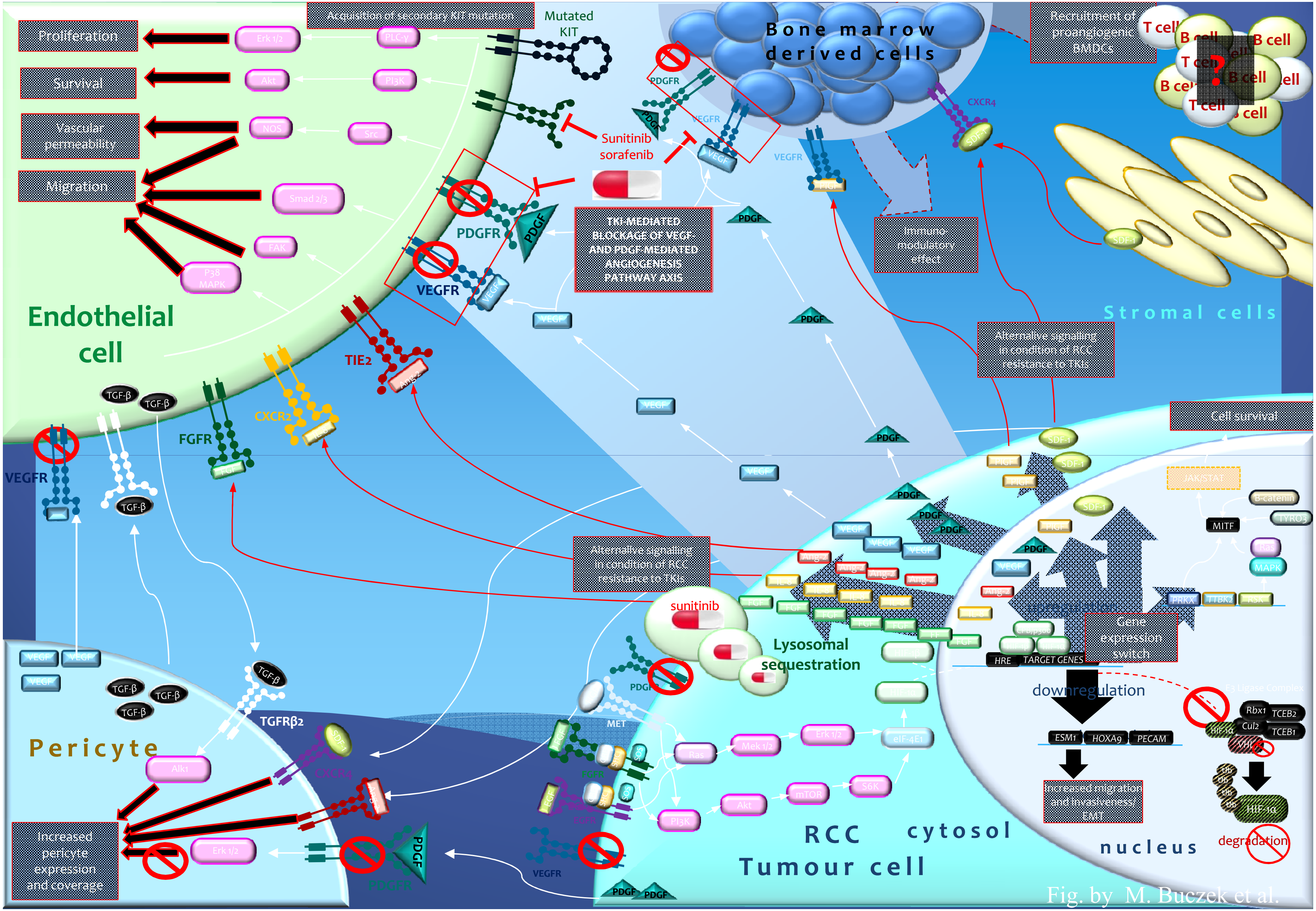
Linehan WM, et al. *J Urol* 2003


A Biopsy Sites
R1 (G3)
R2 (G3)
R3 (G4)
R4 (G1)
R5 (G4)
R9
R6 (G1)
R7 (G4)
R8 (G4)
Hilum
10 cm
Lung metastases
M2a
M2b
Chest-wall metastasis
Primary tumor
Perinephric metastasis
M1


B Regional Distribution of Mutations
Ubiquitous
Shared primary
Shared metastasis
Private
M2b
M2a
M1
R4
R9
R8
R5
R3
R2
R1
PreM
PreP

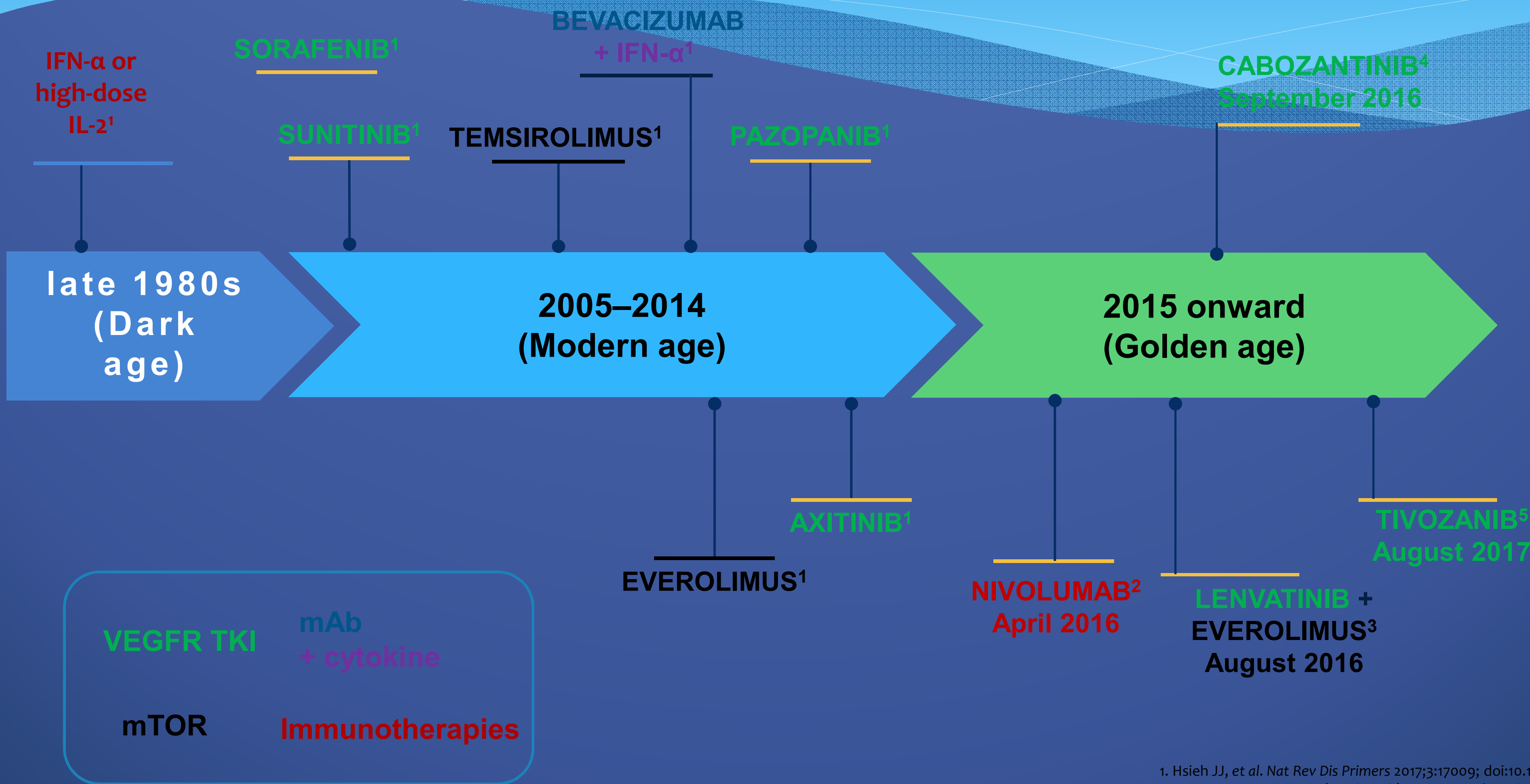

C Phylogenetic Relationships of Tumor Regions
Ubiquitous
Shared primary
Shared metastasis
Private
Normal tissue
VHL
SETD2 (frameshift)
KDM5C (missense and frameshift)
mTOR (missense)
SETD2 (splice site)
?
SETD2 (missense)
KDM5C (splice site)
R1
R2
R3
R5
R8
R9
PreP
R4b
R4a
M1
M2a
M2b
PreM


D Ploidy Profiling
R2
R4
Tetraploid
R9
M2b
DI=1.43
DI=1.81
No. of Cells
Propidium Iodide Staining



Proliferation
Survival
Vascular permeability
Migration
Acquisition of secondary KIT mutation
Mutated KIT
Bone marrow derived cells
Recruitment of proangiogenic BMDCs
Sunitinib sorafenib
PDGFR
VEGFR
PDGF
VEGF
TKI-MEDIATED BLOCKAGE OF VEGF- AND PDGF-MEDIATED ANGIOGENESIS PATHWAY AXIS
Immuno-modulatory effect
CXCR4
SDF-1
Stromal cells
Endothelial cell
TIE2
CXCR2
FGFR
TGF-β
Alternative signalling in condition of RCC resistance to TKIs
Cell survival
sunitinib
Lysosomal sequestration
upregulation
Gene expression switch
downregulation
HRE
TARGET GENES
ESM1
HOXA9
PECAM
Increased migration and invasiveness/ EMT
MITF
PRKX
TTBK2
RSK
Rbx1
TCEB2
Cul2
TCEB1
HIF-1α
degradation
Pericyte
TGFRβ2
MET
Increased pericyte expression and coverage
RCC
cytosol
Tumour cell
nucleus
Fig. by M. Buczek et al.

New therapies have ushered in a golden age of aRCC treatment, transforming outcomes

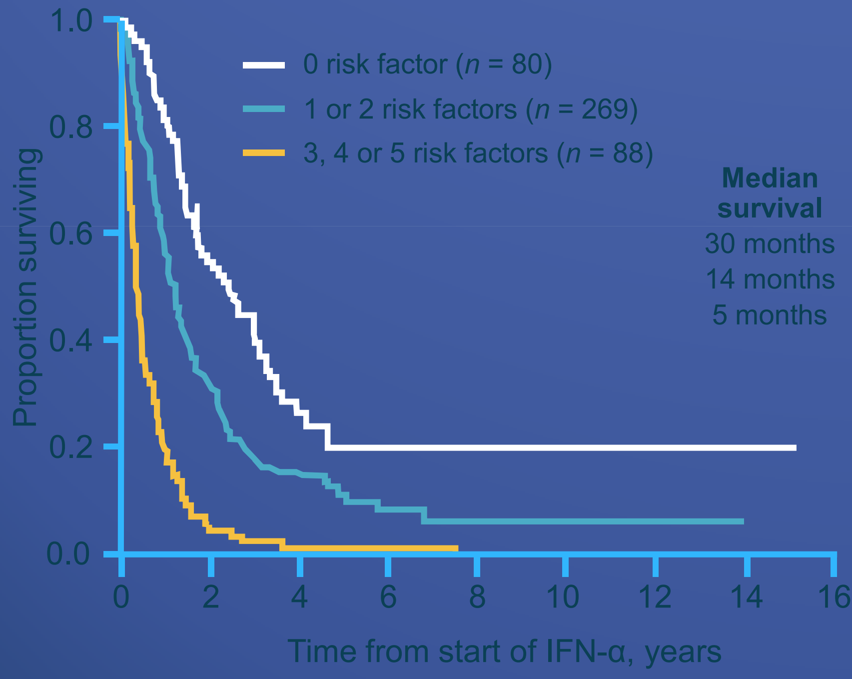


IFN, interferon; IL, interleukin; mAb, monoclonal antibody; mTOR, mechanistic target of rapamycin; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

1. Hsieh JJ, *et al. Nat Rev Dis Primers* 2017;3:17009; doi:10.1038/nrdp.2017.9 .
2. Opdivo® (nivolumab) Summary of Product Characteristics.
3. Kisplyx® (lenvatinib) Summary of Product Characteristics.
4. Cabometyx® (cabozantinib) Summary of Product Characteristics. October 2016.
5. AVEO Oncology press release. August 2017. http://investor.aveooncology.com/phoenix.zhtml?c=219651&p=irol-newsArticle_Print&ID=2296788. Accessed 31 August 2017

Targeted therapies have improved OS in mRCC

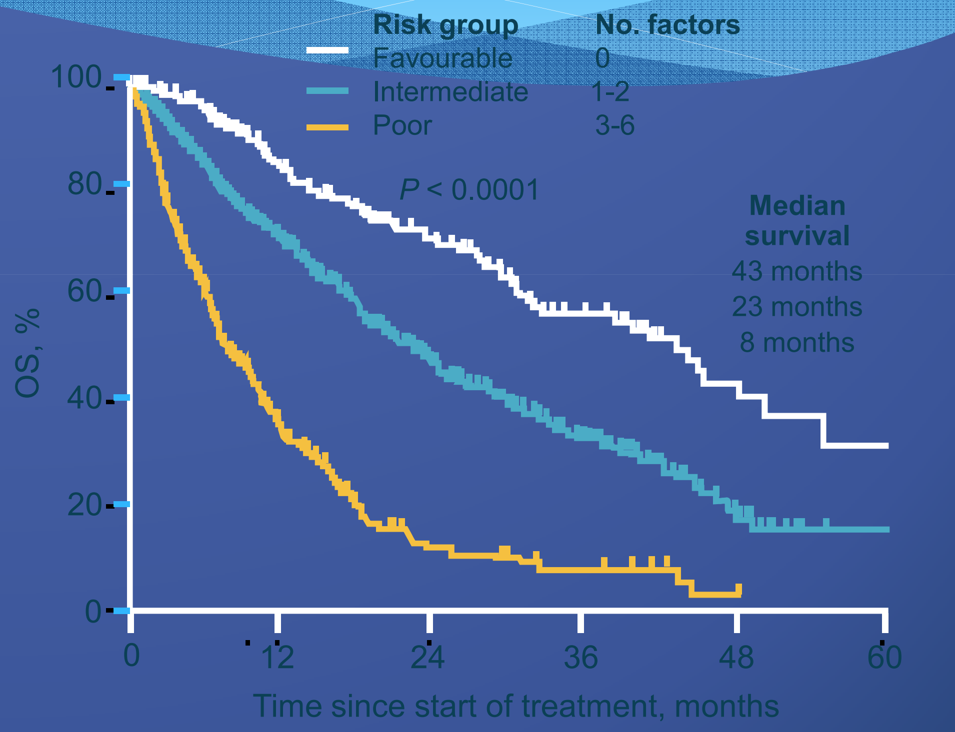
Before VEGF-targeted therapies (IFN-α)



*Risk factors KPS <80%, time from diagnosis to IFN-α <1 year, low serum haemoglobin, high corrected calcium (>2.5 mmol/liter [10 mg/dl]), high LDH (>1.5× ULN).

Motzer RJ et al. J Clin Oncol. 2002;20:289-296.

VEGF-targeted therapies



*Risk factors for survival included anaemia, thrombocytosis, neutrophilia, hypercalcaemia, KPS <80%, and <1 year from diagnosis to treatment.

Heng DY et al. Lancet Oncol 2013;14:141-148.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 11, 2007 VOL. 356 NO. 2

Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

Robert J. Motzer, M.D., Thomas E. Hutson, D.O., Pharm.D., Piotr Tomczak, M.D., M. Dror Michaelson, M.D., Ph.D., Ronald M. Bukowski, M.D., Olivier Rixe, M.D., Ph.D., Stéphane Oudard, M.D., Ph.D., Sylvie Negrier, M.D., Ph.D., Cezary Szczylik, M.D., Ph.D., Sindy T. Kim, B.S., Isan Chen, M.D., Paul W. Bycott, Dr.P.H., Charles M. Baum, M.D., Ph.D., and Robert A. Figlin, M.D.*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma

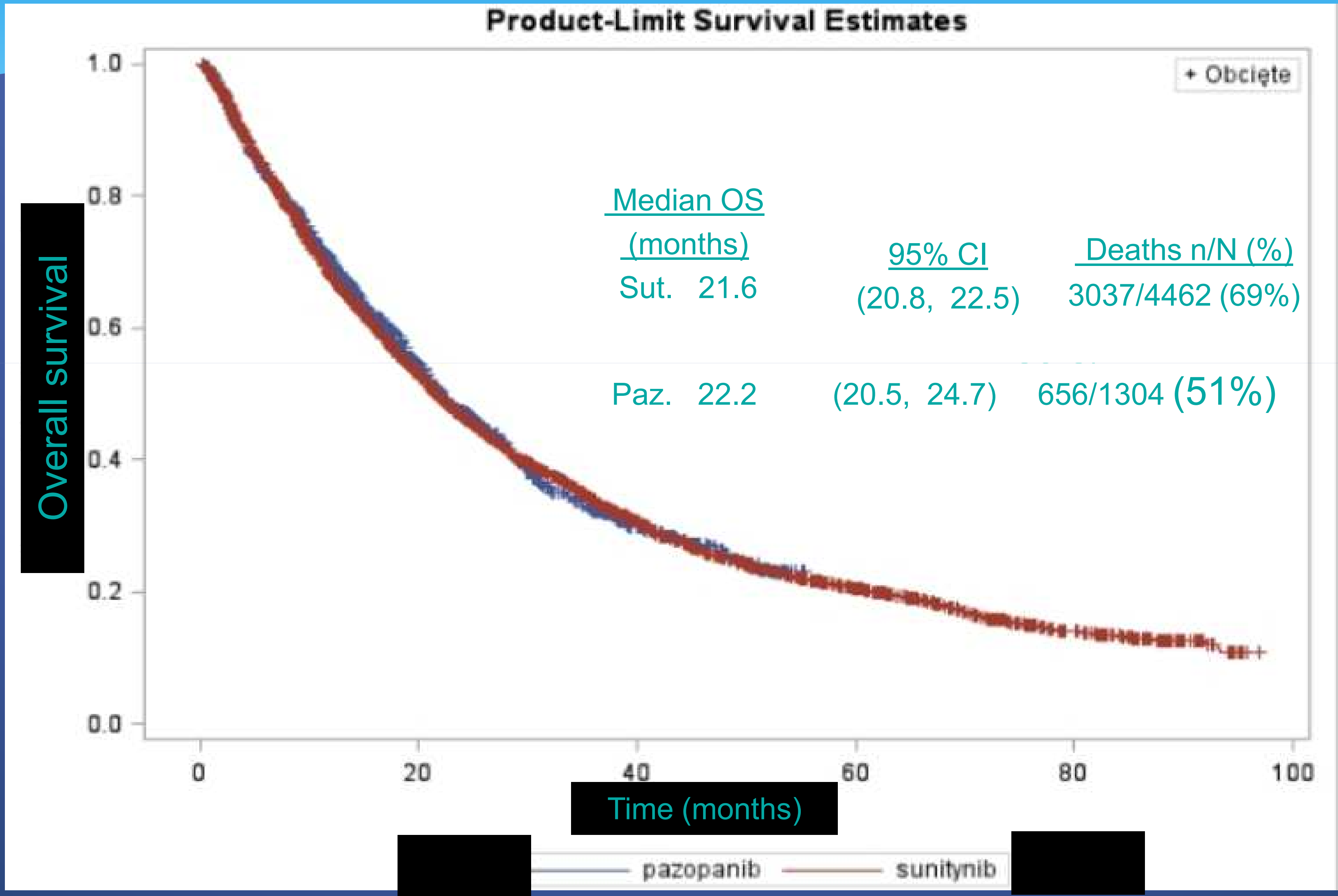
Bernard Escudier, M.D., Tim Eisen, M.D., Walter M. Stadler, M.D., Cezary Szczylik, M.D., Stéphane Oudard, M.D., Michael Siebels, M.D., Sylvie Negrier, M.D., Christine Chevreau, M.D., Ewa Solska, M.D., Apurva A. Desai, M.D., Frédéric Rolland, M.D., Tomasz Demkow, M.D., Thomas E. Hutson, D.O., Pharm.D., Martin Gore, M.D., Scott Freeman, M.D., Brian Schwartz, M.D., Minghua Shan, Ph.D., Ronit Simantov, M.D., and Ronald M. Bukowski, M.D., for the TARGET Study Group*

CONCLUSIONS

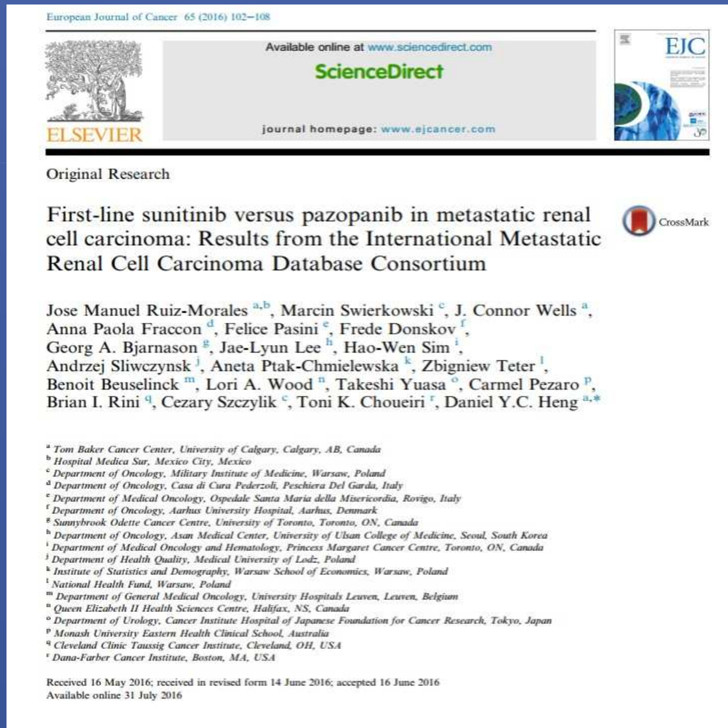
As compared with placebo, treatment with sorafenib prolongs progression-free survival in patients with advanced clear-cell renal-cell carcinoma in whom previous therapy has failed; however, treatment is associated with increased toxic effects.

NEJM, January 11, 2007

OVERALL SURVIVAL – SUNITINIB vs PAZOPANIB



The superiority battle in first line is over



European Journal of Cancer 65 (2016) 102–108

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

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Original Research

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

CrossMark

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,*]

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[b] Hospital Medica Sur, Mexico City, Mexico
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[k] Institute of Statistics and Demography, Warsaw School of Economics, Warsaw, Poland
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[m] Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium
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[q] Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA
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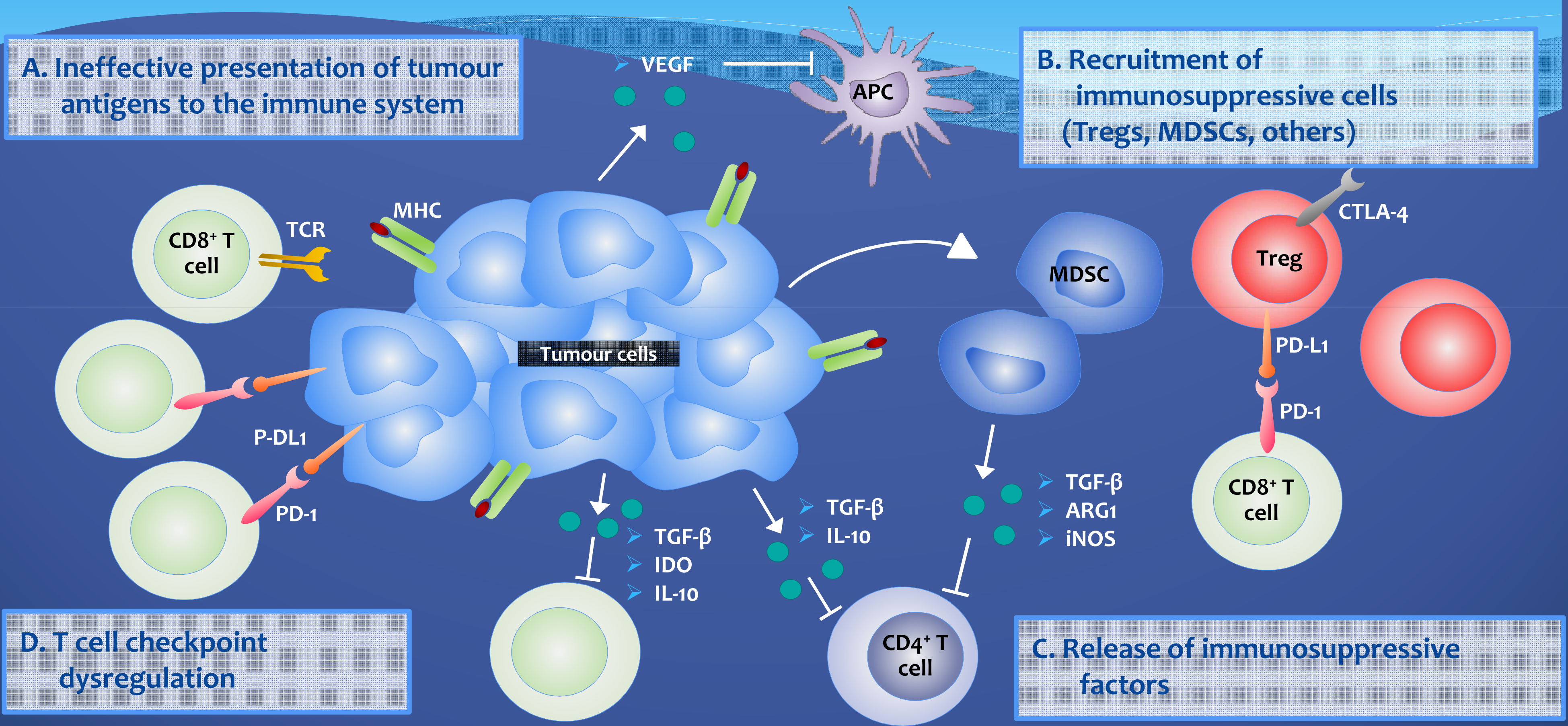
Available online 31 July 2016

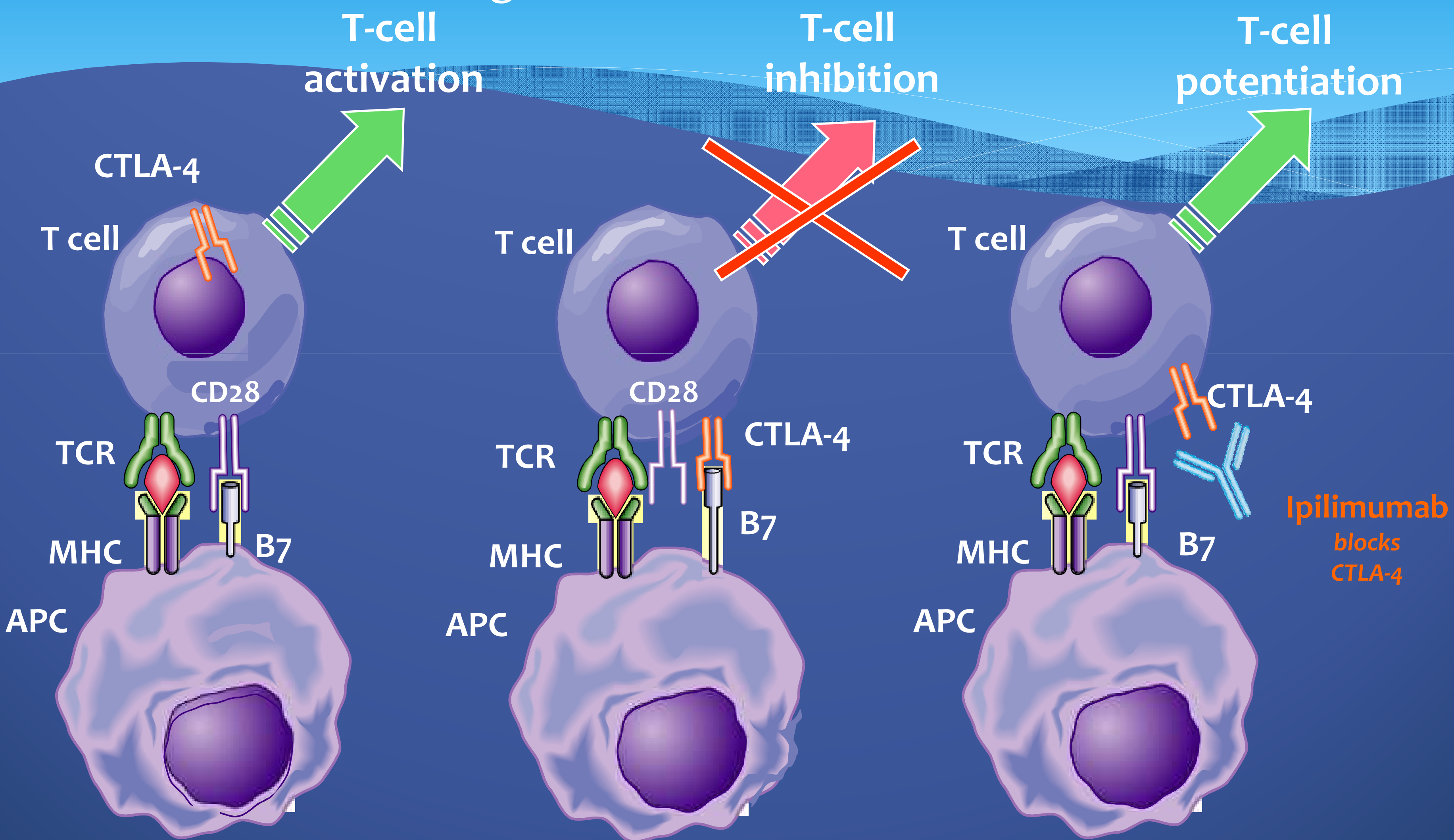
Tumours use various mechanisms to escape the immune system

Immune escape mechanisms are complex and frequently overlapping



Vesely MD, et al. *Ann Rev Immunol* 2011;29:235–271

Ipilimumab, a CTLA-4 blocking human monoclonal antibody, augments T-cell activation

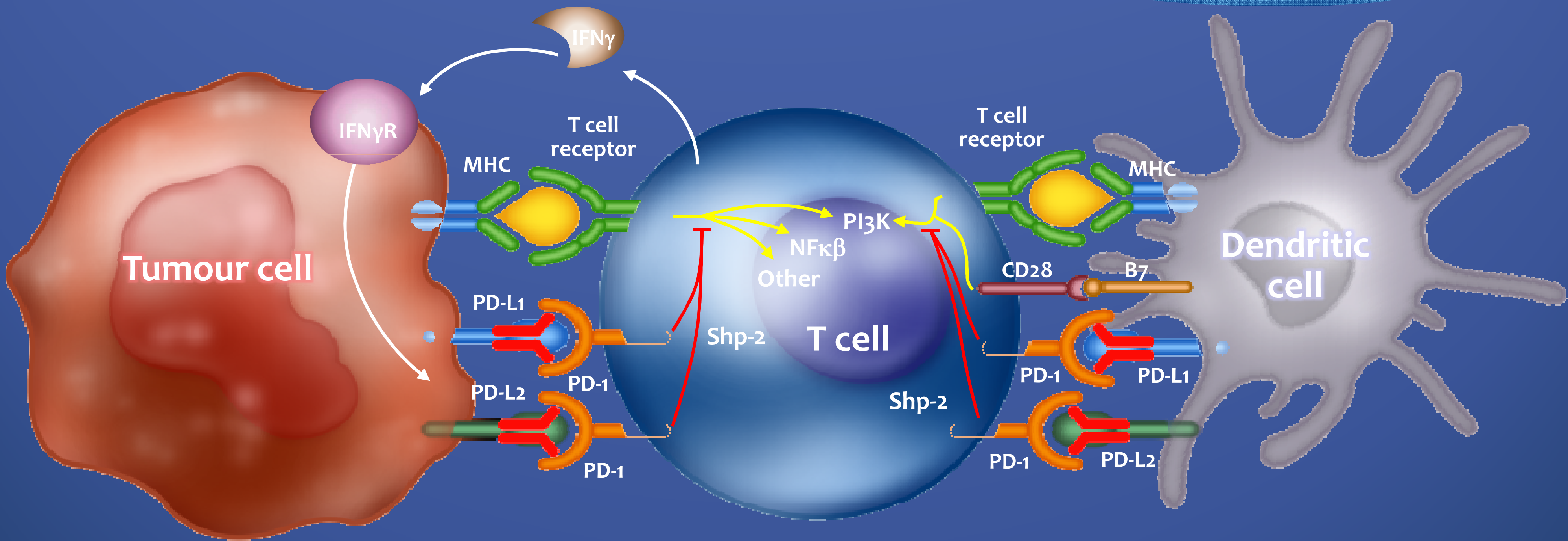


Adapted from Weber J. *Cancer Immunol Immunother* 2009;58:823

Role of PD-1 pathway in suppressing antitumour immunity

Recognition of tumour by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 upregulation on tumour

Priming and activation of T cells through MHC/antigen and CD28/B7 interactions with antigen-presenting cells



Nivolumab is a PD-1 receptor blocking antibody

Ribas A. *N Engl J Med* 2012;366(26):2517–2519

Nivolumab anti PD-1: CheckMate-025 study design (n=822)

Previously treated mRCC

Patients

- Confirmed clear-cell advanced/metastatic RCC
- Measurable disease (RECIST)
- Karnofsky PS ≥70%
- 1–2 previous regimens of antiangiogenic therapy
- Progressed during or ≤6 months of last regimen

Stratification factors

- Region
- MSKCC risk group
- Number of prior anti-angiogenic therapies

Randomize 1:1

Nivolumab
3 mg/kg intravenously every two weeks

Everolimus
10 mg orally once daily

Primary endpoint

- OS

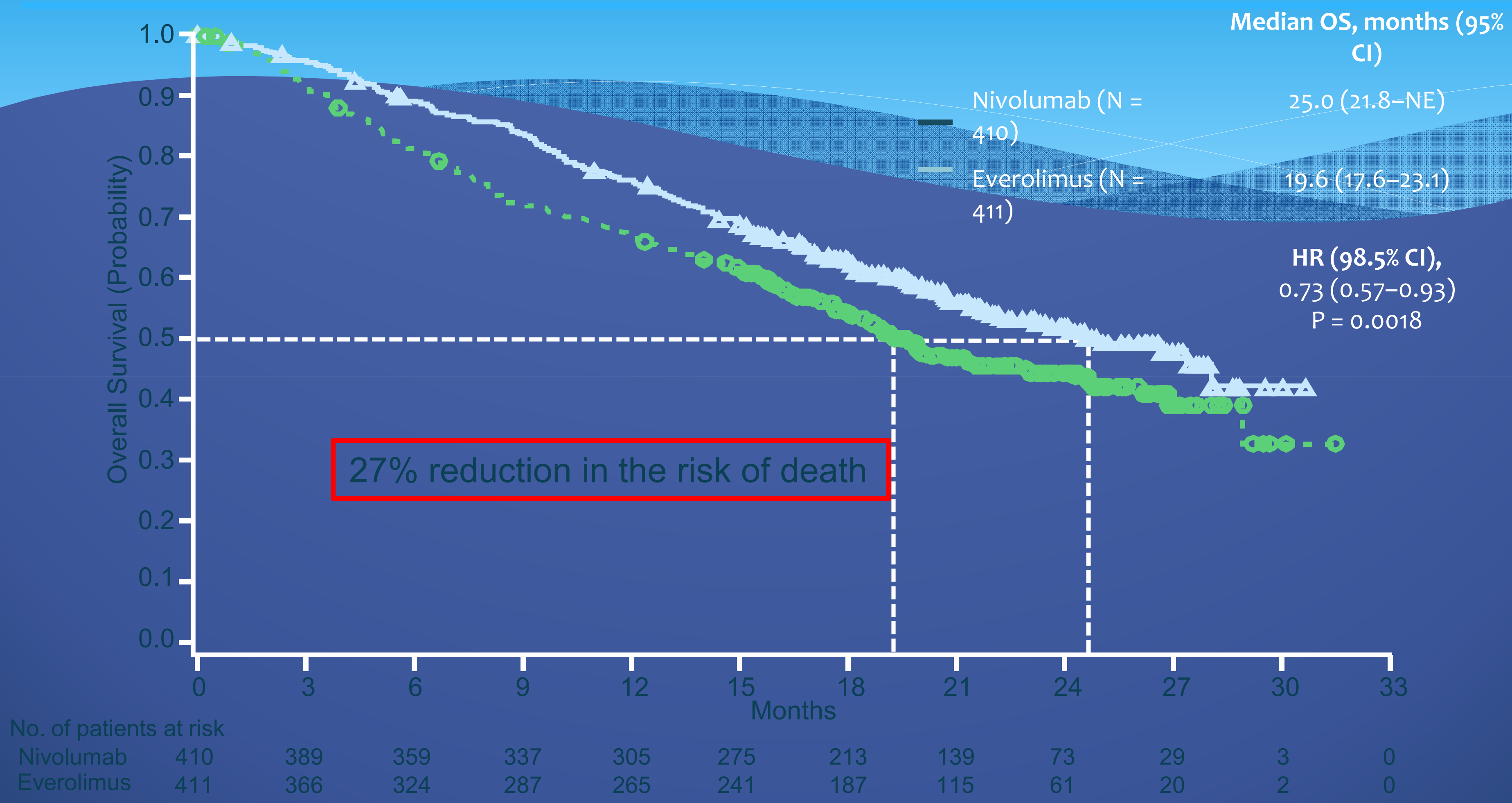
Secondary endpoints

- PFS, ORR and safety

* Treatment beyond progression was permitted if drug was tolerated and clinical benefit was noted

Motzer R et al, N Engl J Med. 2015 Nov 5;373(19):1803-13

Overall survival



* Minimum follow-up was 14 months

CI, confidence interval; HR, hazard ratio; NE, not estimable.

Motzer R et al, N Engl J Med. 2015 Nov 5;373(19):1803-13

LBA5

CheckMate 214: Efficacy and Safety of Nivolumab Plus Ipilimumab vs Sunitinib for Treatment-Naïve Advanced or Metastatic Renal Cell Carcinoma, Including IMDC Risk and PD-L1 Expression Subgroups

Bernard Escudier,[1] Nizar M. Tannir,[2] David F. McDermott,[3] Osvaldo Arén Frontera,[4] Bohuslav Melichar,[5] Elizabeth R. Plimack,[6] Philippe Barthelemy,[7] Saby George,[8] Victoria Neiman,[9] Camillo Porta,[10] Toni K. Choueiri,[11] Thomas Powles,[12] Frede Donskov,[13] Pamela Salman,[14] Christian K. Kollmannsberger,[15] Brian Rini,[16] Sabeen Mekan,[17] M. Brent McHenry,[17] Hans J. Hammers,[18] Robert J. Motzer[19]

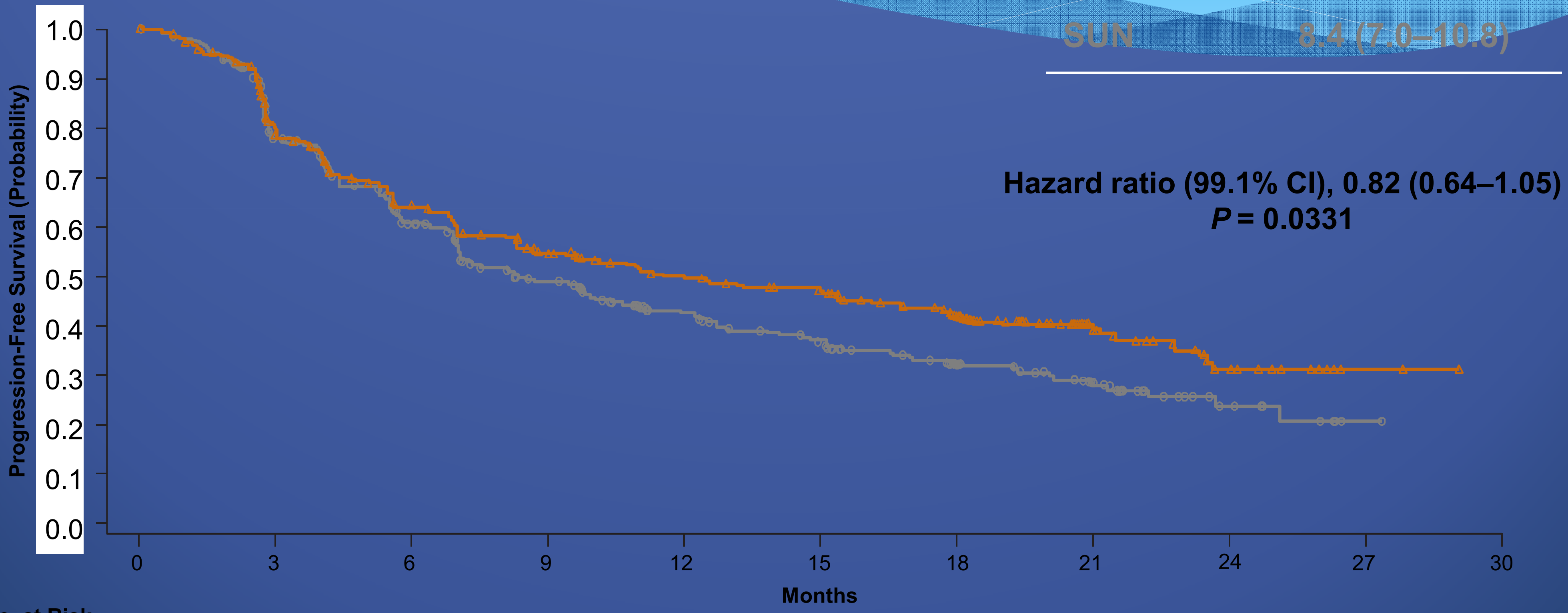
[1]Gustave Roussy, Villejuif, France; [2]University of Texas, MD Anderson Cancer Center Hospital, Houston, TX, USA; [3]Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA, USA; [4]Centro Internacional de Estudios Clinicos, Santiago, Chile; [5]Palacky University, and University Hospital Olomouc, Olomouc, Czech Republic; [6]Fox Chase Cancer Center, Philadelphia, PA, USA; [7]Hôpitaux Universitaires de Strasbourg, Strasbourg, France; [8]Roswell Park Cancer Institute, Buffalo, NY, USA; [9]Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel, and Tel Aviv University, Tel Aviv, Israel; [10]IRCCS San Matteo University Hospital Foundation, Pavia, Italy; [11]Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA; [12]Barts Cancer Institute, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, Royal Free NHS Trust, London, UK; [13]Aarhus University Hospital, Aarhus, Denmark; [14]Fundación Arturo López Pérez, Santiago, Chile; [15]British Columbia Cancer Agency, Vancouver, BC, Canada; [16]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [17]Bristol-Myers Squibb, Princeton, NJ, USA; [18]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins, Baltimore, MD, USA; [19]Memorial Sloan Kettering Cancer Center, New York, NY, USA

1506PL1704348-01; 09.2017

Co-primary endpoint

PFS per IRRC: IMDC intermediate/poor risk

Median PFS, months (95% CI)	
NIVO + IPI	11.6 (8.7–15.5)
SUN	8.4 (7.0–10.8)

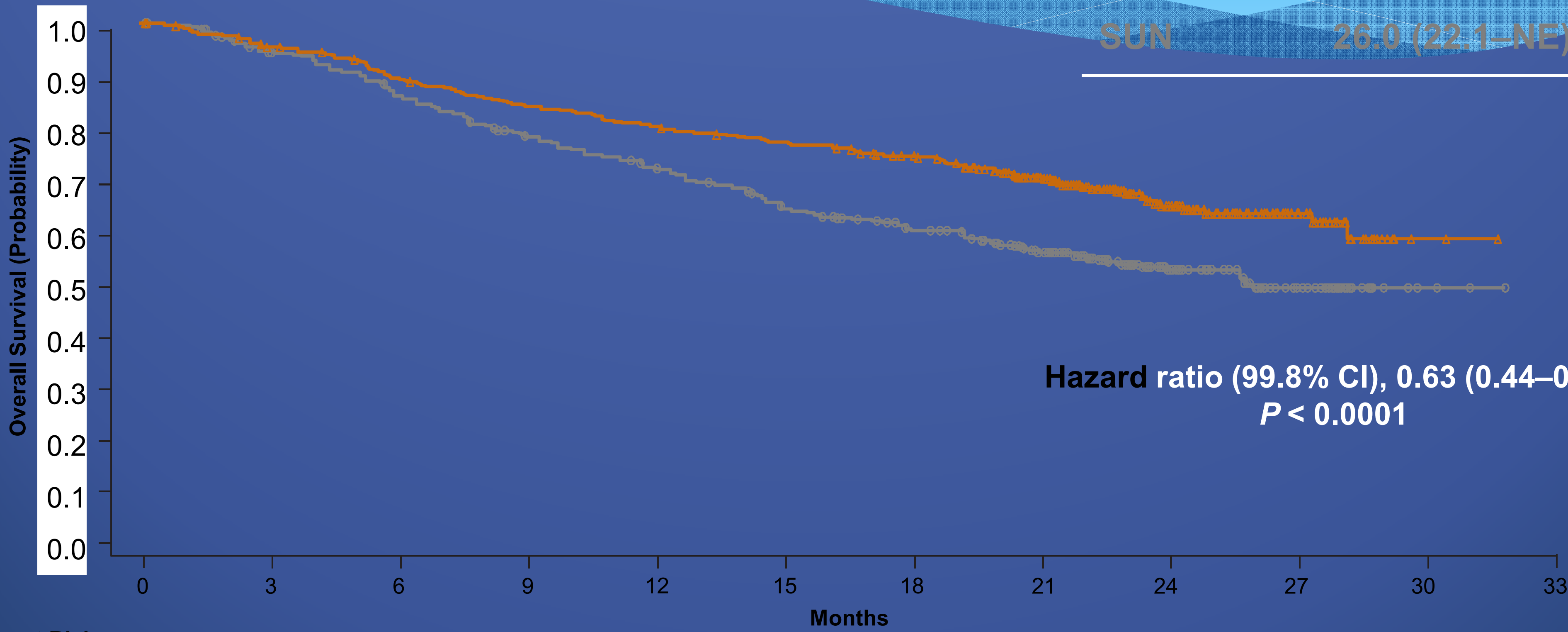


No. at Risk											
NIVO + IPI	425	304	233	187	163	149	118	46	17	3	0
SUN	422	282	191	139	107	86	57	33	11	1	0

Co-primary endpoint

OS: IMDC intermediate/poor risk

	Median OS, months (95% CI)
NIVO + IPI	NR (28.2–NE)
SUN	26.0 (22.1–NE)



No. at Risk												
NIVO + IPI	425	399	372	348	332	318	300	241	119	44	2	0
SUN	422	387	352	315	288	253	225	179	89	34	3	0

Mechanism of resistance of tumor cells to T-cell mediated killing defined

Science RESEARCH ARTICLES

Cite as: D. Pan *et al.*, *Science* 10.1126/science.aao1710 (2018).

A major chromatin regulator determines resistance of tumor cells to T cell-mediated killing

Deng Pan,[1*] Aya Kobayashi,[1*] Peng Jiang,[2*] Lucas Ferrari de Andrade,[1] Rong En Tay,[1] Adrienne Luoma,[1] Daphne Tsoucas,[2] Xintao Qiu,[3] Klothilda Lim,[3] Prakash Rao,[3†] Henry W. Long,[3] Guo-Cheng Yuan,[2] John Doench,[4] Myles Brown,[3] Shirley Liu,[2‡] Kai W. Wucherpfennig[1,5‡]

[1]Department of Cancer Immunology and Virology, Dana-Farber Cancer Institute, Boston, MA 02215, USA. [2]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA 02215, USA. [3]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA. [4]Genetic Perturbation Platform, Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA. [5]Department of Microbiology and Immunobiology, Harvard Medical School, Boston, MA 02115, USA.

*These authors contributed equally to this work. †Present address: Harvard University Office of Technology Development, Cambridge, MA 02138, USA.

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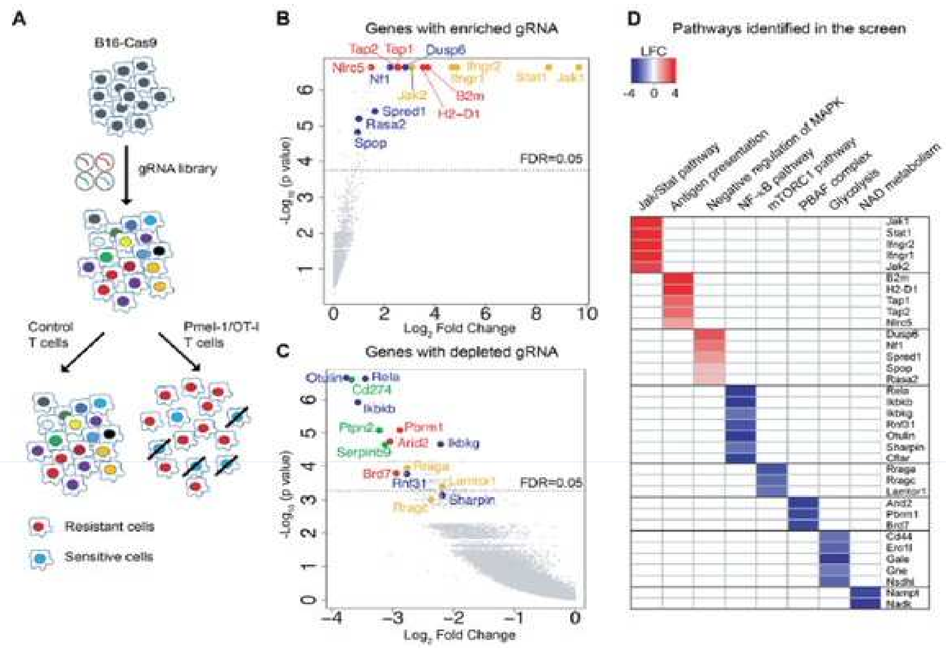
Many human cancers are resistant to immunotherapy for reasons that are poorly understood. We used a genome-scale CRISPR/Cas9 screen to identify mechanisms of tumor cell resistance to killing by cytotoxic T cells, the central effectors of anti-tumor immunity. Inactivation of >100 genes sensitized mouse B16F10 melanoma cells to killing by T cells, including *Pbrm1*, *Arid2* and *Brd7*, which encode components of the PBAF form of the SWI/SNF chromatin remodeling complex. Loss of PBAF function increased tumor cell sensitivity to interferon-γ, resulting in enhanced secretion of chemokines that recruit effector T cells. Treatment-resistant tumors became responsive to immunotherapy when *Pbrm1* was inactivated. In many human cancers, expression of *PBRM1* and *ARID2* inversely correlated with expression of T cell cytotoxicity genes, and *Pbrm1*-deficient murine melanomas were more strongly infiltrated by cytotoxic T cells.

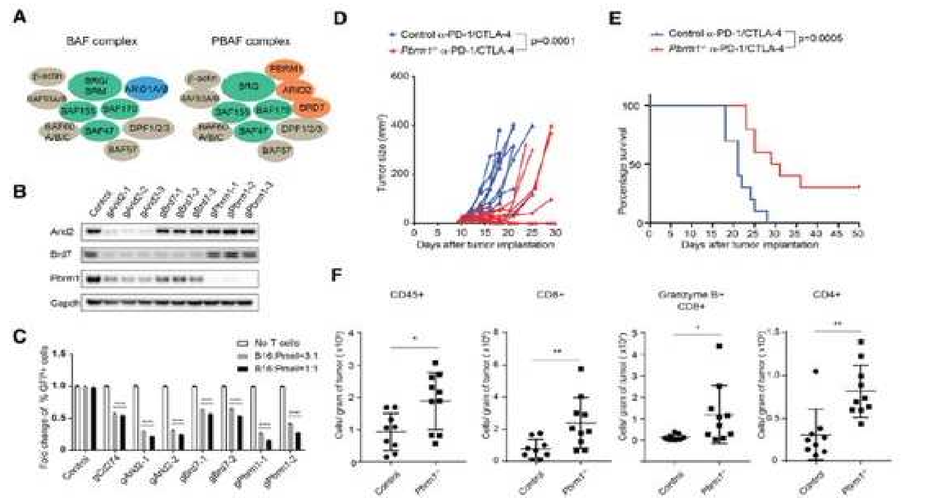
Cancer immunotherapies that target inhibitory receptors on T cells including the PD-1 receptor, can induce durable responses, but the majority of patients do not respond (*1*). The mechanisms that determine resistance to these immunotherapies remain poorly understood. Cytotoxic T cells are key effectors of tumor immunity based on their ability to detect and kill transformed cells following T cell receptor (TCR) recognition of peptide antigens bound to MHC class I proteins (*2*). T cell-mediated cytotoxicity can be remarkably efficient, but it is diminished when MHC class I expression by tumor cells is reduced. Cytotoxicity is also inhibited when tumor cells express PD-L1, the ligand for the PD-1 receptor on T cells (*3*). We hypothesized that sensitivity and resistance of tumor cells to T cell-mediated attack is dynamically regulated by multiple pathways in tumor cells that could represent novel targets for immunotherapy.

Discovery of tumor cell-intrinsic genes regulating sensitivity and resistance to T cell-mediated killing

Tumor cells transduced with a genome-scale gRNA library were subjected to selection with cytotoxic T cells to identify genes that controlled resistance to T cell-mediated killing (Fig. 1A). We selected the murine B16F10 melanoma cell line for this screen because it is resistant to checkpoint blockade with antibodies targeting the PD-1 and/or CTLA-4 receptors (*4*, *5*). Inactivation of resistance genes resulted in depletion of the corresponding gRNAs, but such depletion could only be detected with sufficient sensitivity when most tumor cells had sufficient Cas9 activity. We therefore selected a B16F10-Cas9 clone with high editing efficiency (fig. S1) and tested it with positive controls that were either more resistant (*B2m*$^{-/-}$) or sensitive (*Cd274*$^{-/-}$) to T cell-mediated cytotoxicity (fig. S2). This B16F10-Cas9 clone was then transduced with a genome-scale gRNA library in a lentiviral vector (*6*). Selection was performed either with Pmel-1 T cells which have a relatively low TCR affinity for an endogenous melanoma antigen (*7*) or high-affinity OT-I T cells (*8*). Edited tumors cells were selected by three-day co-culture with Pmel-1 CD8 T cells (or one day for OT-I T cells), and the representation of all gRNAs was quantified by Illumina sequencing of the gRNA cassette (Fig. 1A). The specificity of gRNA enrichment/depletion was demonstrated by comparing selection with tumor-specific T cells versus control T cells of irrelevant specificity (fig. S3). This comparison also controlled for potential effects of gRNAs on cell proliferation/viability.

A number of genes known to be essential for T cell-mediated tumor immunity were identified among the enriched gRNAs in both Pmel-1 and OT-1 screens (Fig. 1B, fig. S4A, tables S1-2), including key genes in the MHC class I and IFNγ signaling pathways (*9*-*11*). Mutations in both MHC and interferon pathway genes were shown to confer resistance to cancer immunotherapy (*12*, *13*). T cell-based CRISPR/Cas9 screens have been described by two other la-





SWI/SNF who it is

* (SWItch/Sucrose Non-Fermentable) – nucleosome/chromatin remodelling complex found in both eukaryotes and prokaryotes – its components are encoded by different genes among them
* ARID2, PBRM1, BRD7
* SWI/SNF job – is to open up stretches of thightly wound DNA, to make possible to be read

Breakthrough in 2nd line, some data in first

ORIGINAL ARTICLE

Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

T.K. Choueiri, B. Escudier, T. Powles, P.N. Mainwaring, B.I. Rini, F. Donskov, H. Hammers, T.E. Hutson, J.-L. Lee, K. Peltola, B.J. Roth, G.A. Bjarnason, L. Géczi, B. Keam, P. Maroto, D.Y.C. Heng, M. Schmidinger, P.W. Kantoff, A. Borgman-Hagey, C. Hessel, C. Scheffold, G.M. Schwab, N.M. Tannir, and R.J. Motzer, for the METEOR Investigators*

News Release

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<< Back

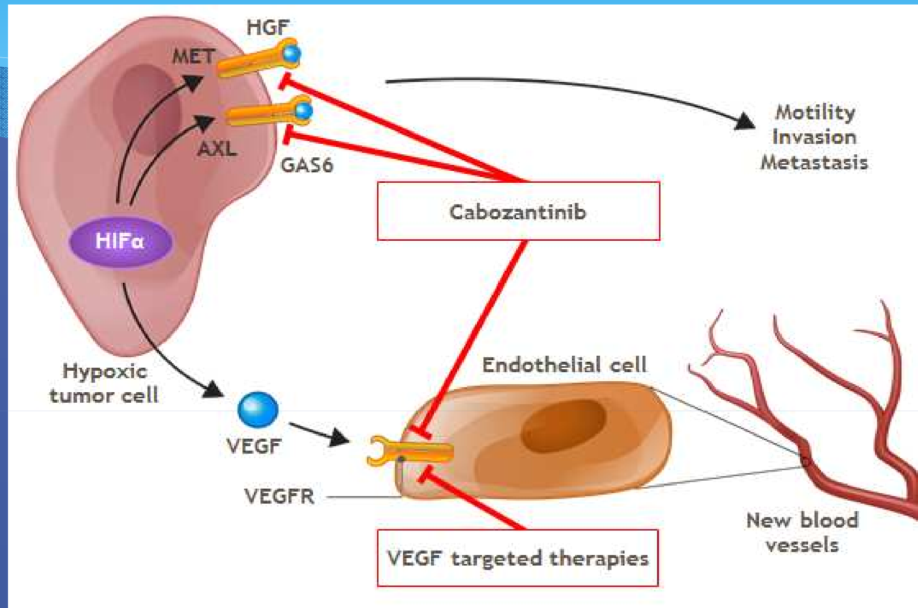
Exelixis Announces Results from Randomized Phase 2 Trial CABOSUN Demonstrate Cabozantinib Significantly Improved Progression-Free Survival versus Sunitinib in Previously Untreated Advanced Renal Cell Carcinoma

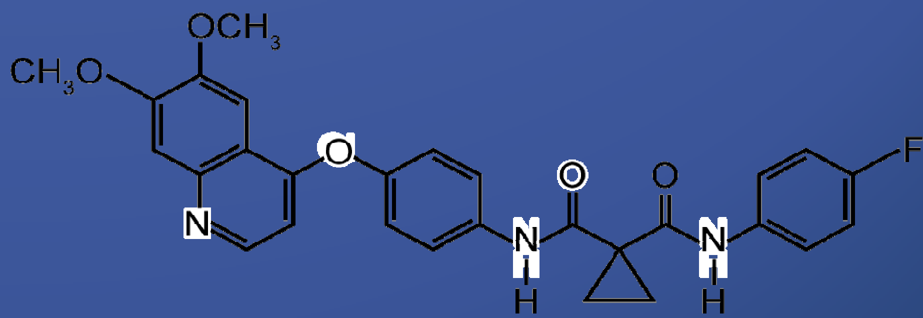
– Exelixis to consult with regulatory authorities to determine next steps in development and submission strategy for cabozantinib in first-line renal cell carcinoma –

SAN FRANCISCO--(BUSINESS WIRE)--May 23, 2016-- Exelixis, Inc. (NASDAQ:EXEL) today announced positive top-line results from the CABOSUN randomized phase 2 trial of cabozantinib in patients with previously untreated advanced renal cell carcinoma (RCC). The trial met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in progression-free survival (PFS) for cabozantinib compared with sunitinib in patients with advanced intermediate- or poor-risk RCC. The safety data in the cabozantinib-treated arm of the study were consistent with those observed in previous studies in patients with advanced RCC. CABOSUN is being conducted by The Alliance for Clinical Trials in Oncology as part of Exelixis' collaboration with the National Cancer Institute's Cancer Therapy Evaluation Program (NCI-CTEP). The final results from CABOSUN will be submitted for presentation at a future medical conference.

Cabozantinib Targets Multiple Distinct Pathways

- Cabozantinib is an oral small molecule inhibitor of multiple tyrosine kinase receptors, including:
  - MET
  - AXL
  - VEGFR-1, VEGFR-2, VEGFR-3
- Cabozantinib, by targeting more than just the VEGF pathway, provides a multi-targeted approach for the treatment of RCC
  - This may help to overcome resistance to VEGFR inhibition

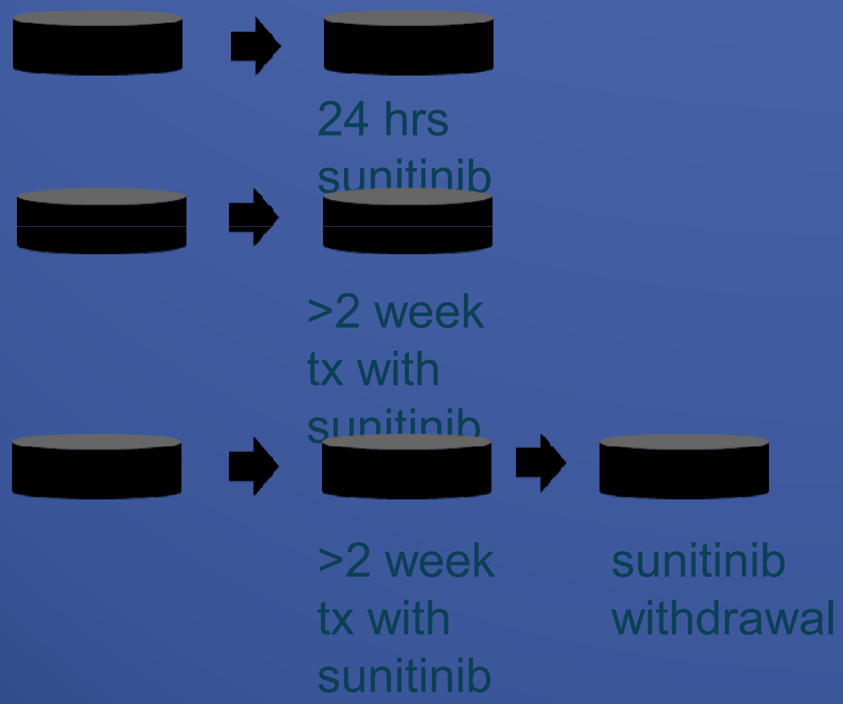


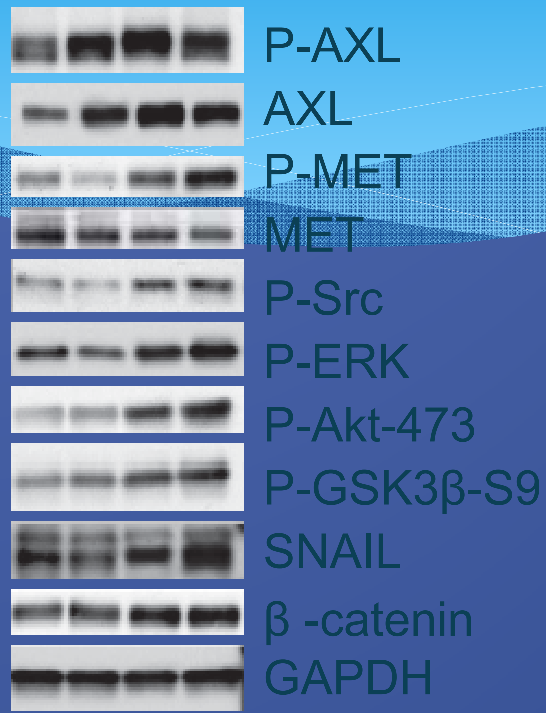


1. Yakes MF, et al. Mol Cancer Ther 2011;10:2298–2308

Chronic sunitinib treatment induces AXL and MET in RCC cell lines

786-0 Cell Line





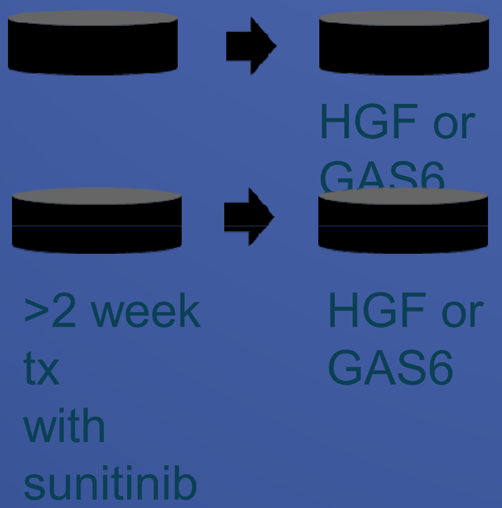
+Suni(24h)		+		
Chronic Suni			+	+
-Suni				+

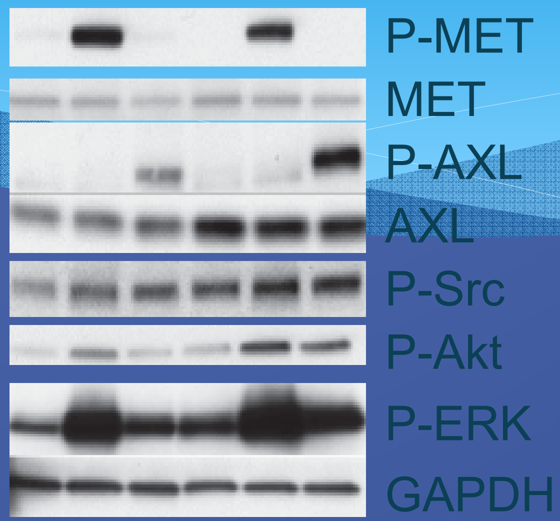
Tx = treatment

Zhou L, et al. Oncogene 2016; 35:2687-97

Chronic sunitinib treatment increases sensitivity to induces AXL and MET ligands

786-0 Cell Line

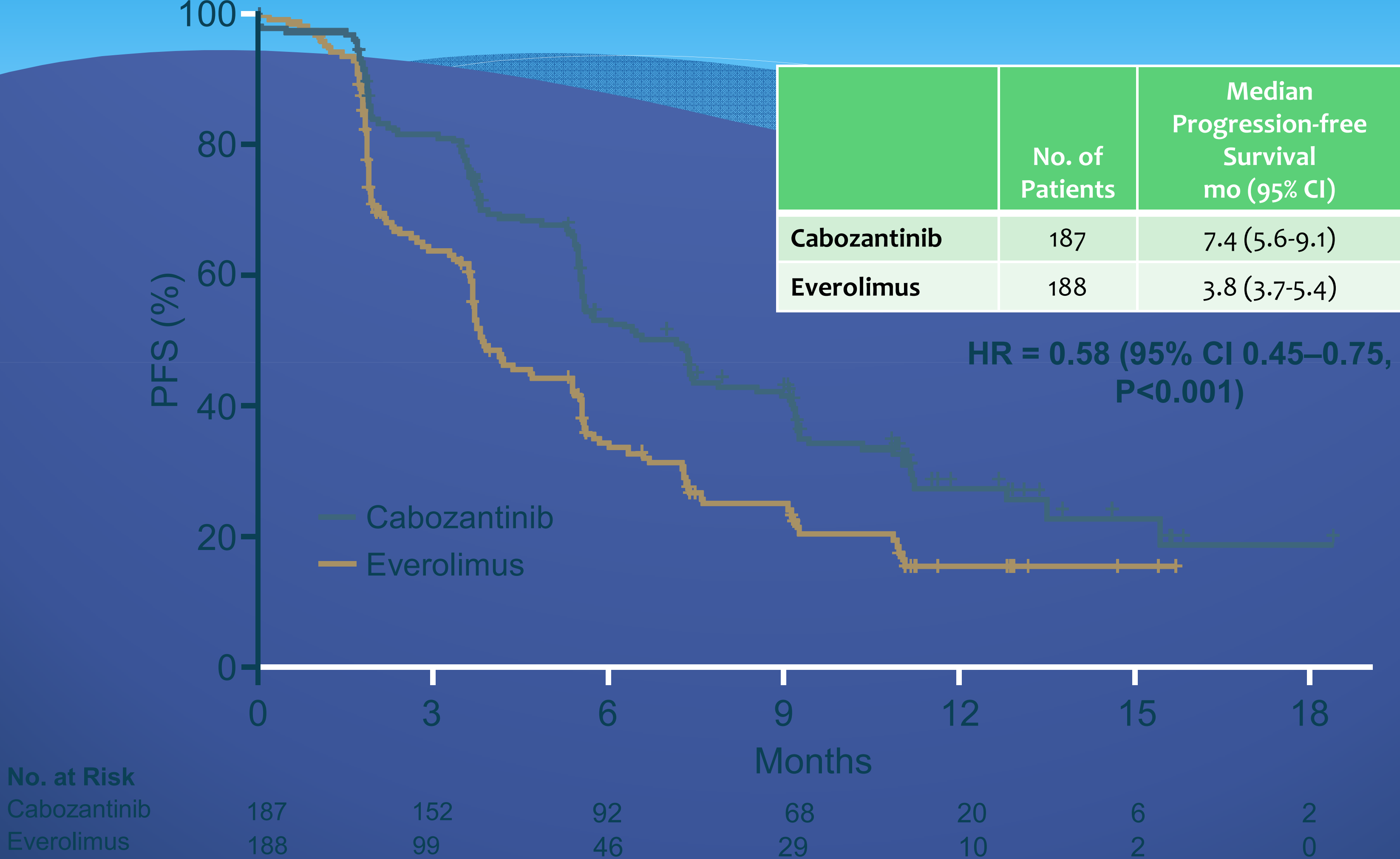




Chronic Suni				+	+	+
-Suni				+	+	+
HGF		+			+	
GAS6			+			+

Zhou L, et al. Oncogene 2016; 35:2687-97

Phase 3 METEOR Study: Primary Endpoint of PFS (Independent Review – PFS Population)



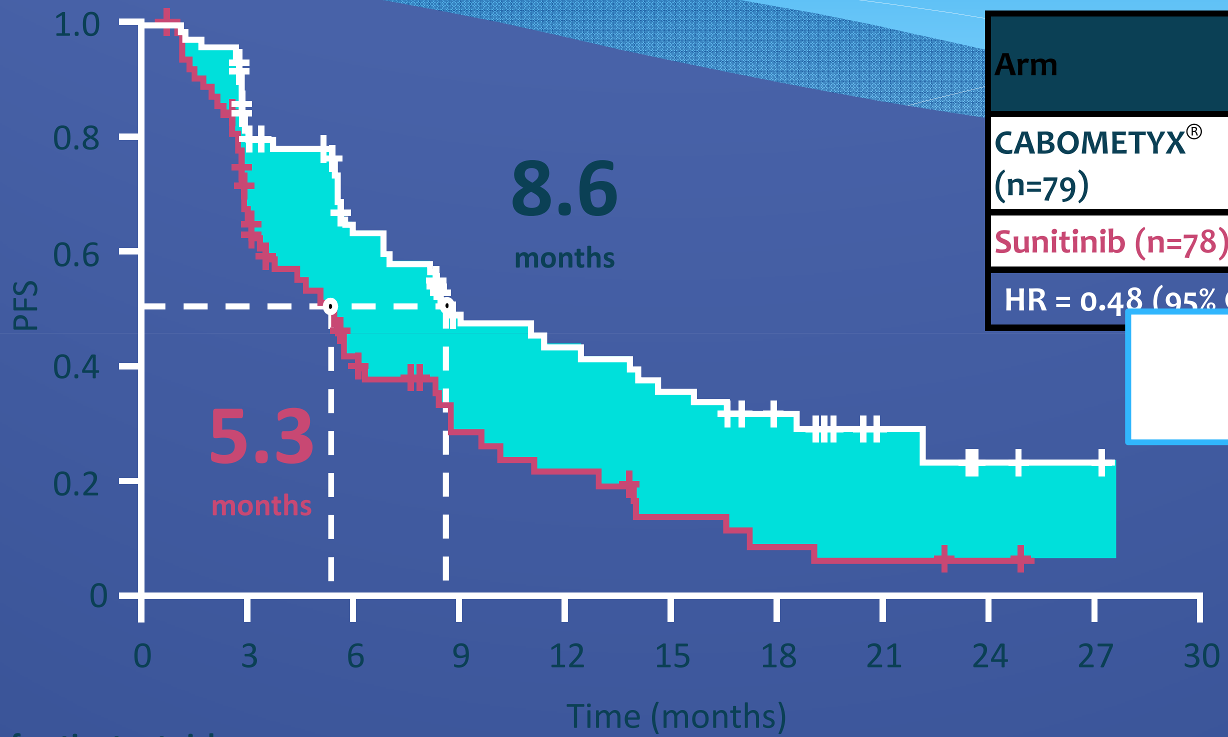
	No. of Patients	Median Progression-free Survival mo (95% CI)	No. of Events
Cabozantinib	187	7.4 (5.6-9.1)	121
Everolimus	188	3.8 (3.7-5.4)	126

Data cut-off: 22 May 2015

Choueiri TK, et al. N Engl J Med 2015;373:1814–23

CABOMETYX® Increased Median PFS Compared with Sunitinib (Independent Review)

CABOSUN Phase 2 Trial: PFS by Independent Review Committee



Arm	**Median**, mo (95% CI)
CABOMETYX® (n=79)	
Sunitinib (n=78)	
HR = 0.48 (95% CI 0.31–0.74) p=0.0008	

No. of patients at risk

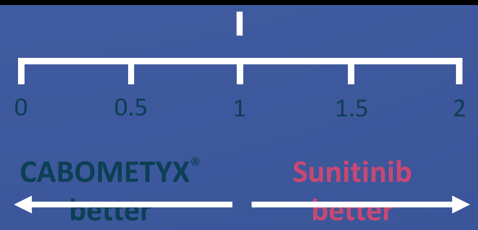
CABOMETYX®	79	51	37	24	22	18	12	5	2	1	0
Sunitinib	78	36	21	12	9	5	3	2	1	0	0

* Data cut-off: September 15, 2016
* Choueiri TK, et al. Presented at ESMO 2017 [Abstract LBA38].

Subgroup Analysis Showed Consistent PFS Benefit of CABOMETYX® Compared with Sunitinib (Investigator Assessment)

CABOSUN Phase 2 Trial: PFS Subgroup Analysis by Investigator Assessment

	N	Median PFS (months)			HR (95% CI)
		CABOMETYX®	Sunitinib		
All patients	157	8.21	5.59		
IMDC risk group					
Intermediate	127	8.31	6.24		
Poor	30	6.14	2.77		
Bone metastases					
No	100	8.64	7.59		
Yes	57	6.14	3.38		



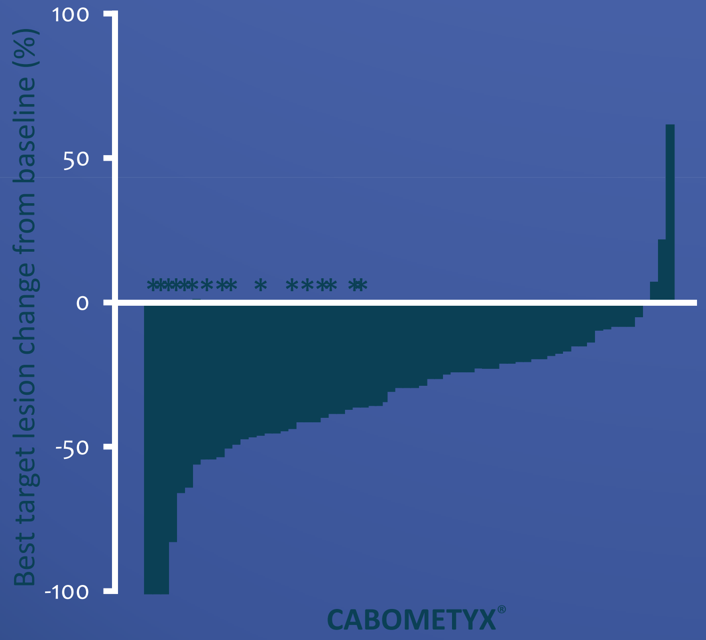
- Choueiri TK, et al. *J Clin Oncol* 2017;35:591–597 ("Errata." J Clin Oncol, 35(32), p. 3736).

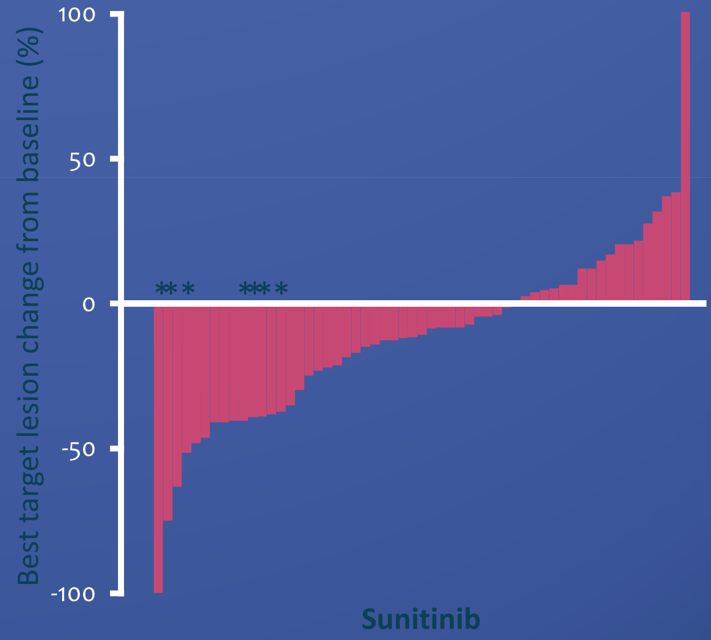
More Patients Experienced Tumour Reduction with CABOMETYX® Compared with Sunitinib (Independent Review)

80% **of CABOMETYX®-treated patients experienced tumour reduction (63/79)**

vs

50% **of sunitinib-treated patients experienced tumour reduction (39/78)**





Not evaluated: n=6

Not evaluated: n=18

CABOSUN Phase 2 Trial: Best Target Lesion Change from Baseline by Independent Review

- *Confirmed partial response

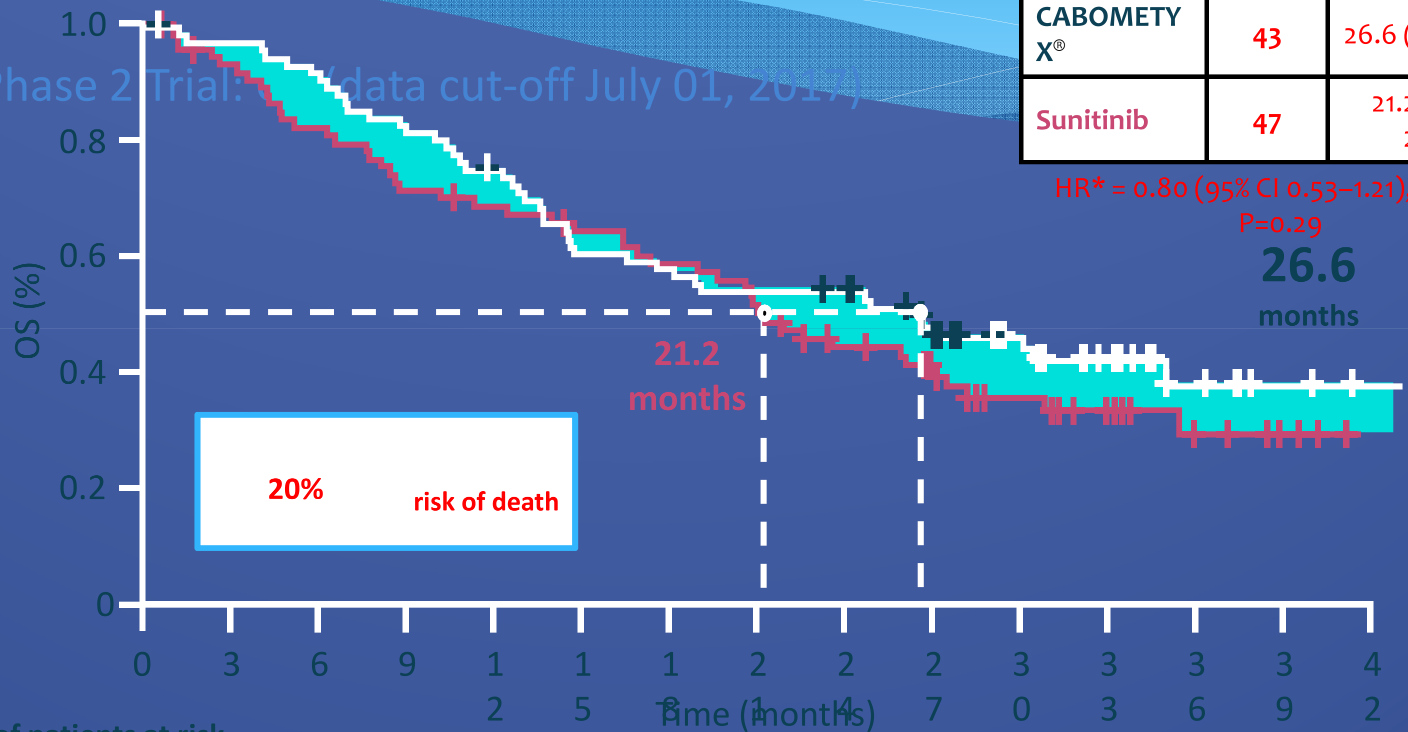
- Choueiri TK, et al. Presented at ESMO 2017 [Abstract LBA38].

CABOMETYX® Extended Median OS by Over 5 Months Compared with Sunitinib

CABOSUN Phase 2 Trial: (data cut-off July 01, 2017)

Arm	Deaths	Median, mo (95% CI)
CABOMETYX®	43	26.6 (14.6–NE)
Sunitinib	47	21.2 (16.3–27.4)

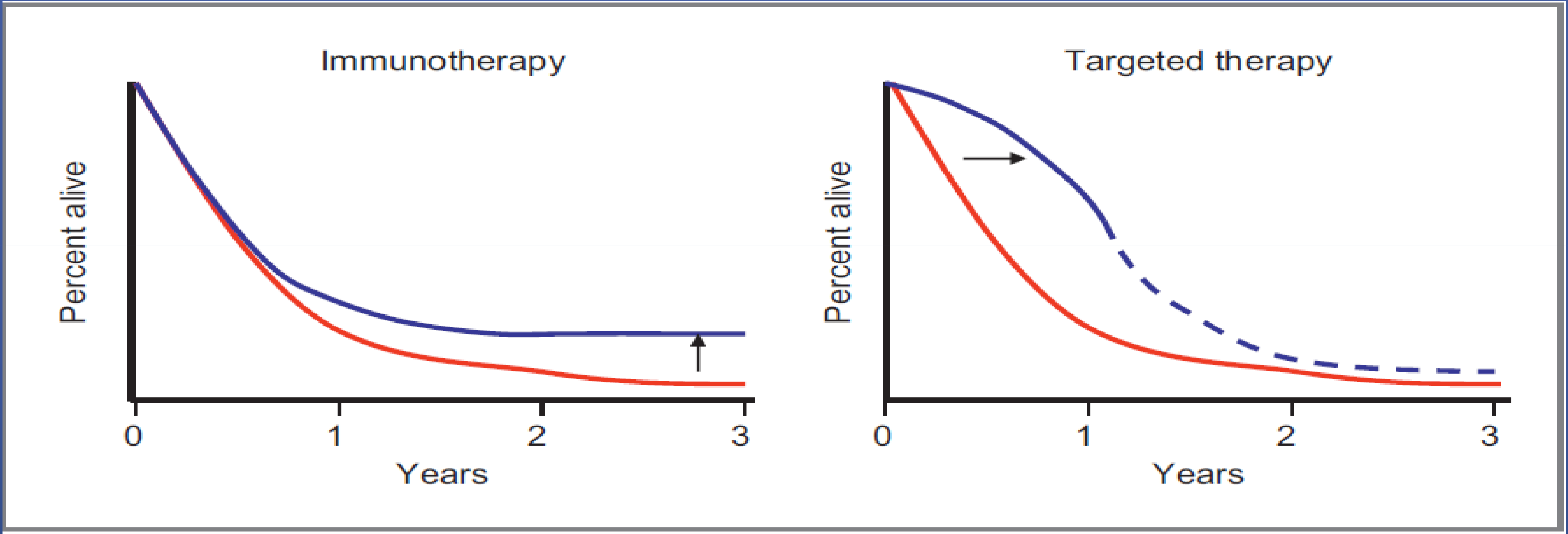
HR* = 0.80 (95% CI 0.53–1.21), 2-sided P=0.29



No. of patients at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
CABOMETYX®	79	76	71	64	58	47	45	42	41	31	23	15	8	4	2
Sunitinib	78	69	61	53	50	46	42	36	29	24	17	12	6	3	0

* Choueiri TK, et al. Presented at ESMO 2017 [Abstract LBA38].

Immunotherapy vs targeted therapy

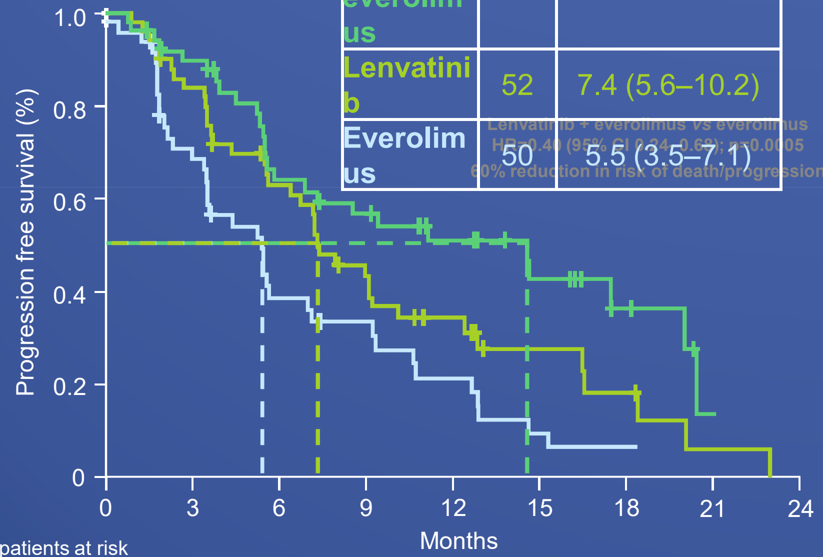


Ribas A, i wsp. *Clin Cancer Res.* 2012;18:336–341; Drake CG. *Ann Oncol.* 2012;23(suppl 8):viii41–viii46.

Lenvatinib + everolimus Phase II study endpoints: Overall survival and progression free survival

Secondary: Progression Free Survival (PFS)

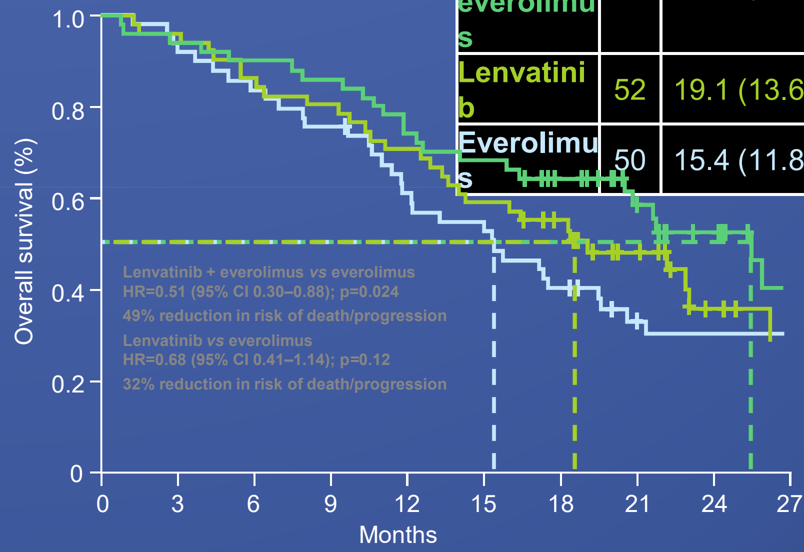
	N	Median PFS, mo (95% CI)
Lenvatinib + everolimus	51	14.6 (5.9–20.1)
Lenvatinib	52	7.4 (5.6–10.2)
Everolimus	50	5.5 (3.5–7.1)



No. of patients at risk	0	3	6	9	12	15	18	21	24
Lenvatinib/eve	51	41	27	23	16	10	5	1	0
Lenvatinib	52	41	29	20	11	6	4	1	0
Everolimus	50	29	15	11	7	3	1	0	0

Overall Survival (OS)*

	N	Median OS, mo (95% CI)
Lenvatinib + everolimus	51	25.5 (16.4–NE)
Lenvatinib	52	19.1 (13.6–26.2)
Everolimus	50	15.4 (11.8–19.6)



No. of patients at risk	0	3	6	9	12	15	18	21	24	27
Lenvatinib/eve	51	48	46	44	38	35	29	21	14	6
Lenvatinib	52	50	45	42	37	31	26	16	7	4
Everolimus	50	46	42	38	30	27	20	14	8	2

- Objective response rate (95% CI): 43% (29–58) for len + eve *vs* 27% for len (16–41) *vs* 6% for eve (1–17)
- Benefits *vs* everolimus: len + eve p<0.0001; len p=0.0067

N=153 patients.
*Data cut-off: 10 December 2014; study not powered for OS.

1. Motzer RJ, *et al. Lancet Oncol* 2015;16:1473–1482

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

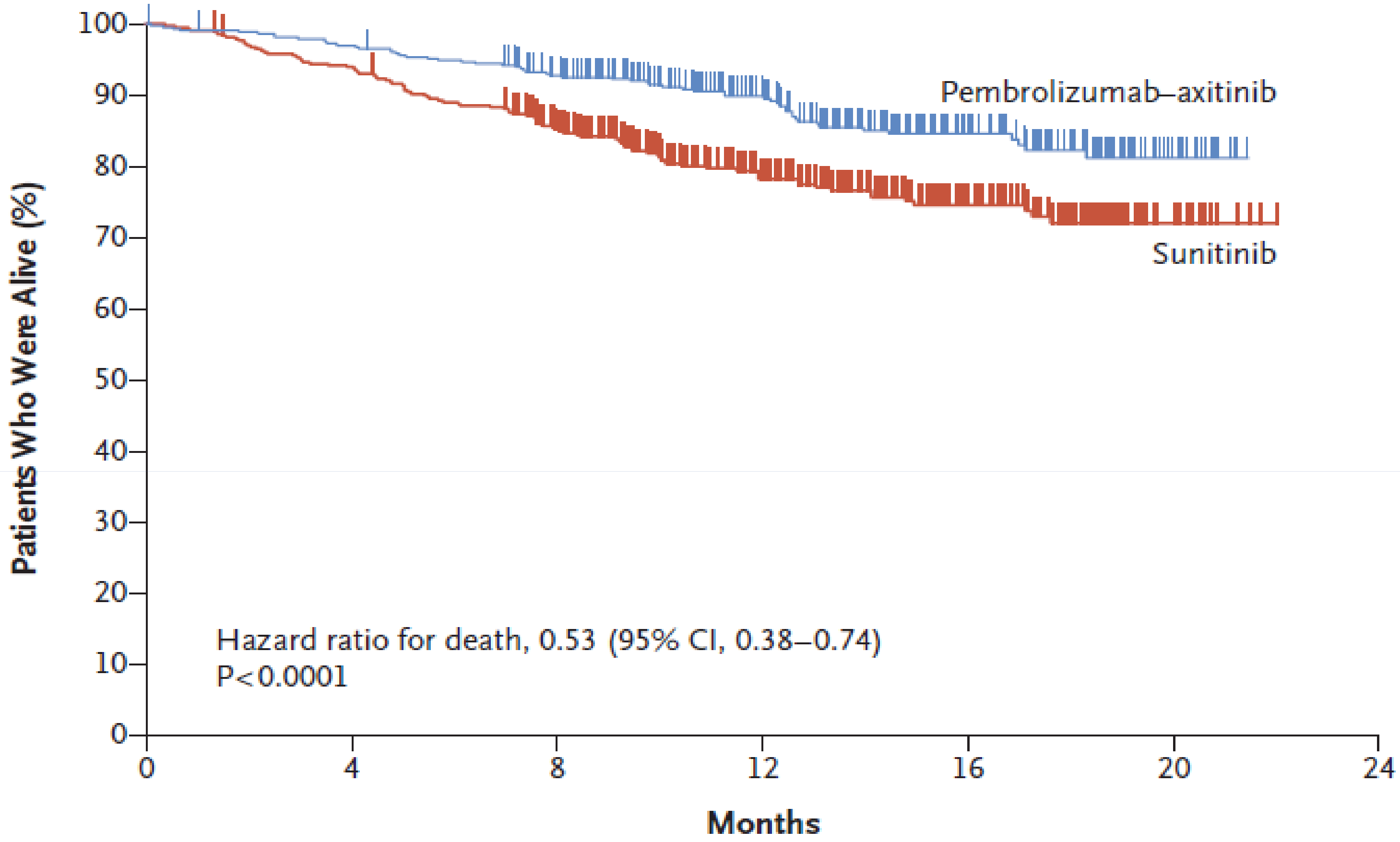
Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

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. Azevedo, D. Borchiellini, C. Szczylik, M. Markus, R.S. McDermott, J. Bedke, S. Tartas, Y.-H. Chang, S. Tamada, Q. Shou, R.F. Perini, M. Chen, M.B. Atkins, and T. Powles, for the KEYNOTE-426 Investigators*

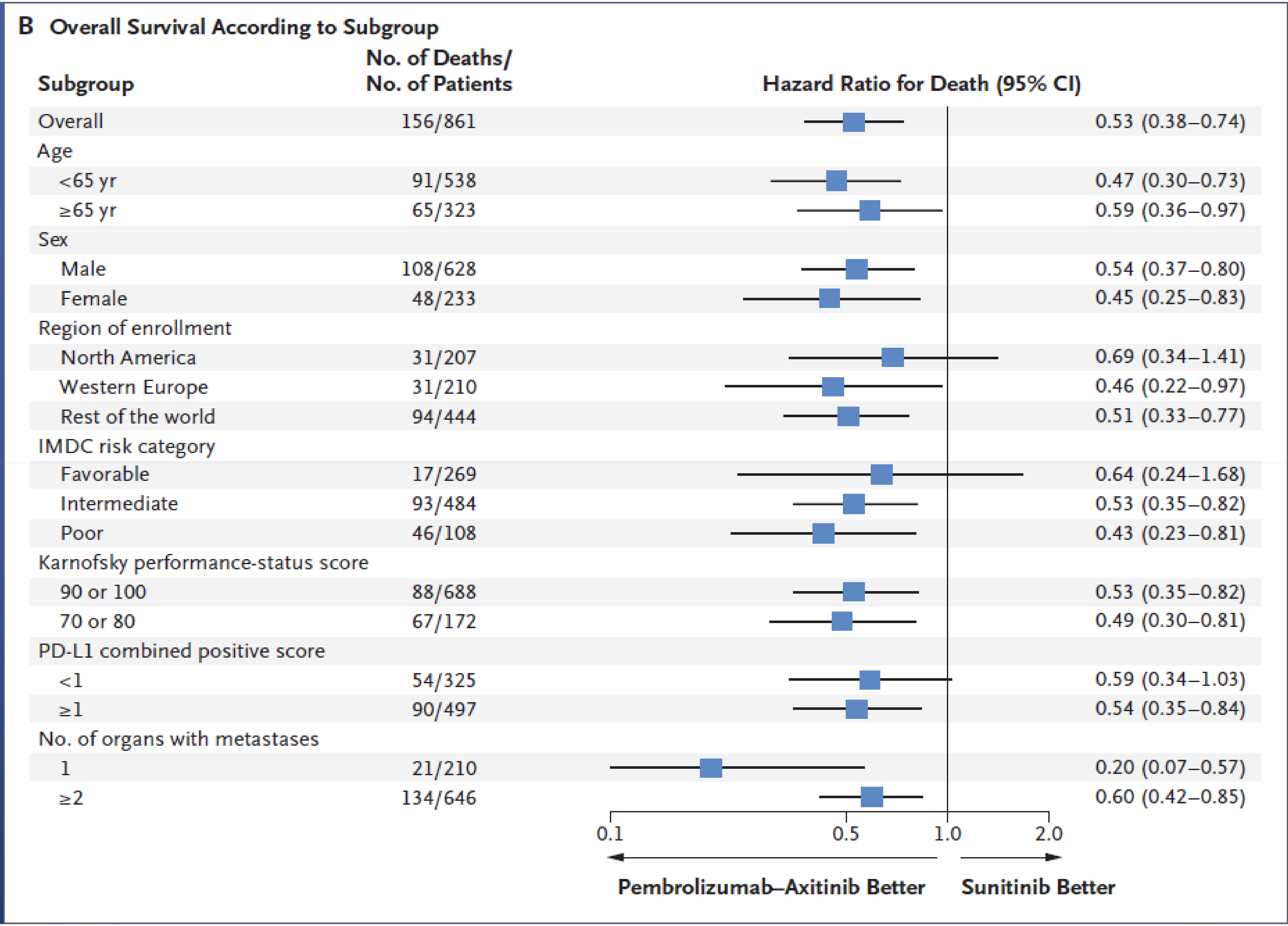
Table 1. Demographic and Disease Characteristics at Baseline.*

Characteristic	Pembrolizumab–Axitinib (N=432)	Sunitinib (N=429)
Age		
Median (range) — yr	62 (30–89)	61 (26–90)
<65 yr — no. (%)	260 (60.2)	278 (64.8)
Male sex — no. (%)	308 (71.3)	320 (74.6)
Region of enrollment — no. (%)		
North America	104 (24.1)	103 (24.0)
Western Europe	106 (24.5)	104 (24.2)
Rest of the world	222 (51.4)	222 (51.7)
IMDC prognostic risk — no. (%)†		
Favorable	138 (31.9)	131 (30.5)
Intermediate	238 (55.1)	246 (57.3)
Poor	56 (13.0)	52 (12.1)
Sarcomatoid features — no./total no. with known status (%)	51/285 (17.9)	54/293 (18.4)
PD-L1 combined positive score — no./total no. with data (%)‡		
≥1	243/410 (59.3)	254/412 (61.7)
<1	167/410 (40.7)	158/412 (38.3)
No. of organs with metastases — no. (%)§		
1	114 (26.4)	96 (22.4)
≥2	315 (72.9)	331 (77.2)
Most common sites of metastasis — no. (%)¶		
Lung	312 (72.2)	309 (72.0)
Lymph node	199 (46.1)	197 (45.9)
Bone	103 (23.8)	103 (24.0)
Adrenal gland	67 (15.5)	76 (17.7)
Liver	66 (15.3)	71 (16.6)
Previous radiotherapy — no. (%)	41 (9.5)	40 (9.3)
Previous nephrectomy — no. (%)	357 (82.6)	358 (83.4)

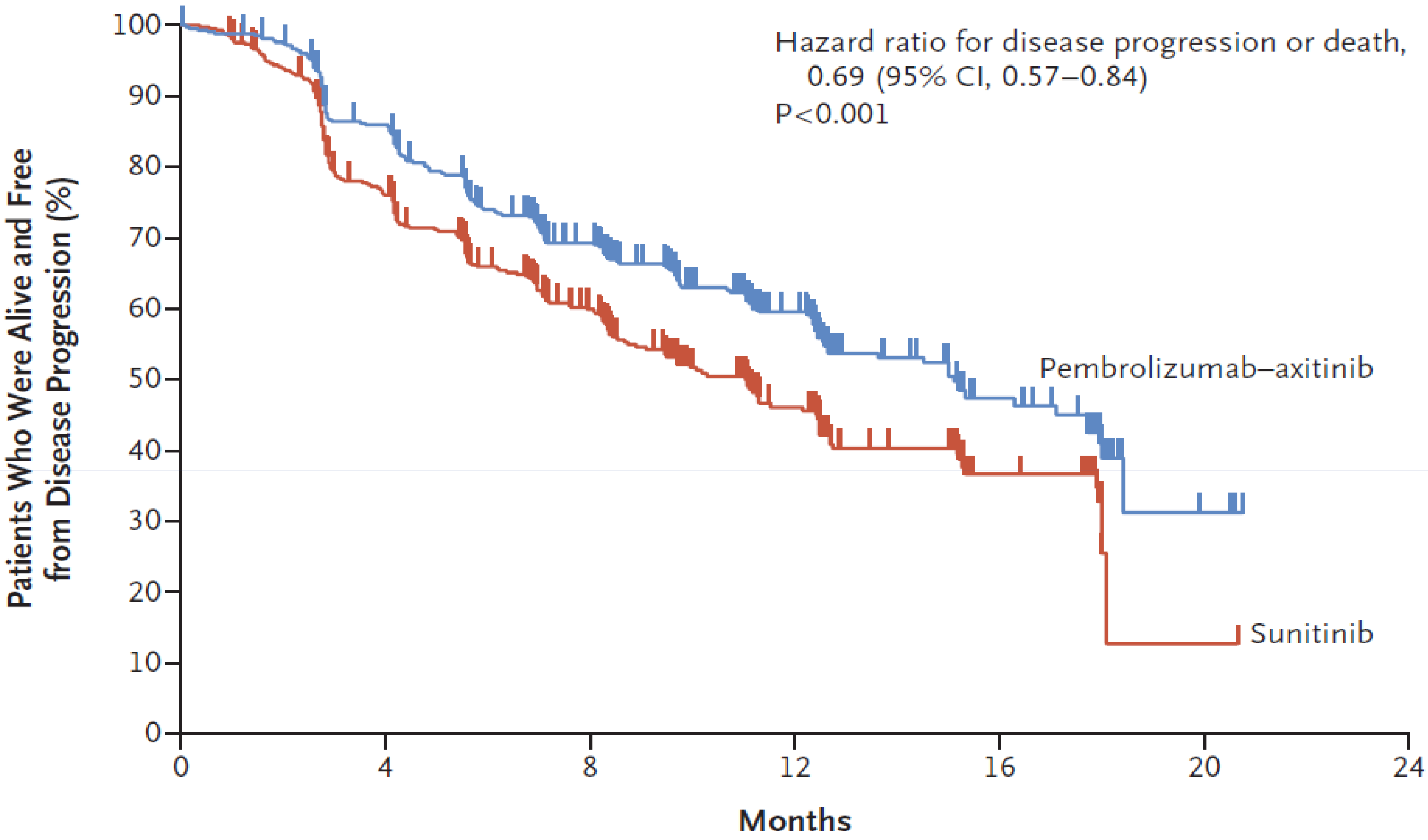
A Overall Survival



No. at Risk							
Pembrolizumab–axitinib	432	417	378	256	136	18	0
Sunitinib	429	401	341	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)
Age
<65 yr 91/538 0.47 (0.30–0.73)
≥65 yr 65/323 0.59 (0.36–0.97)
Sex
Male 108/628 0.54 (0.37–0.80)
Female 48/233 0.45 (0.25–0.83)
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)
No. of organs with metastases
1 21/210 0.20 (0.07–0.57)
≥2 134/646 0.60 (0.42–0.85)
0.1
0.5
1.0
2.0
Pembrolizumab–Axitinib Better
Sunitinib Better

A Progression-free Survival

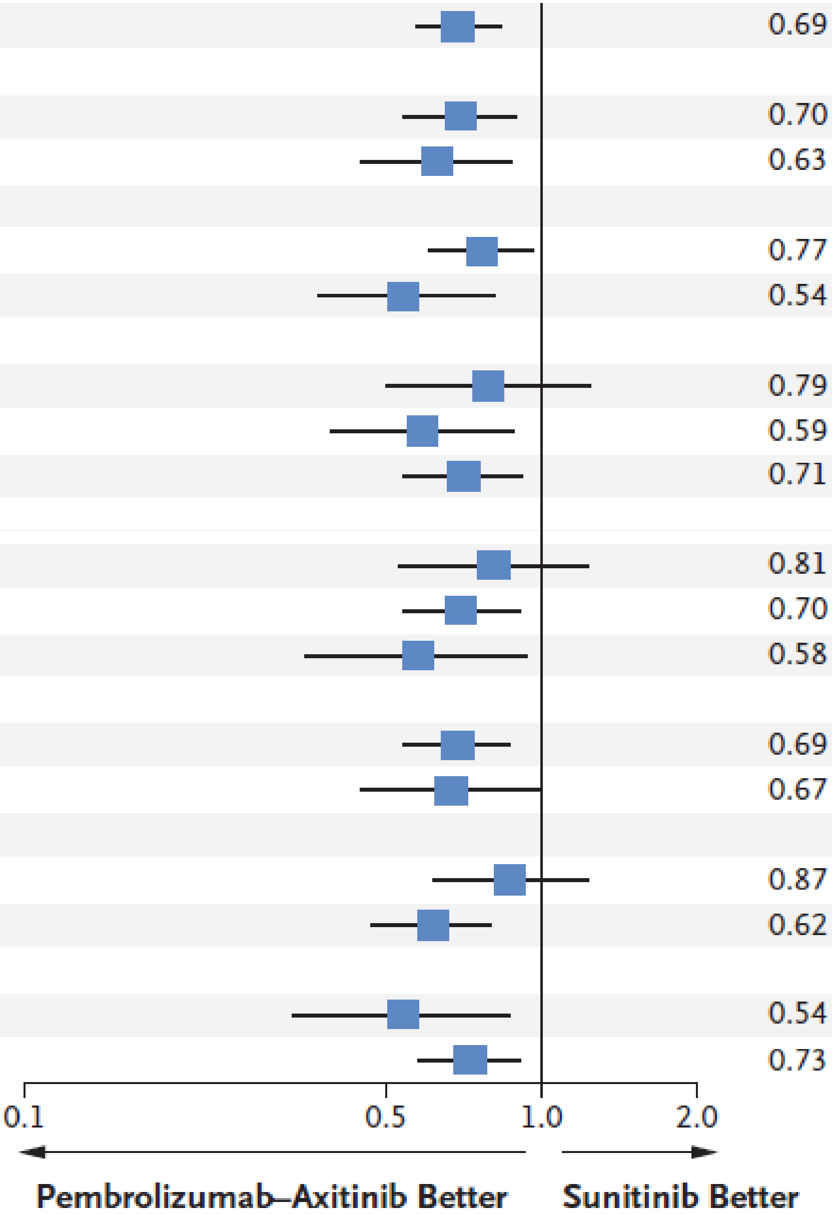


No. at Risk

Pembrolizumab–axitinib	432	357	251	140	42	3	0
Sunitinib	429	302	193	89	29	1	0

B Progression-free Survival According to Subgroup

Subgroup	No. of Instances of Disease Progression or Death/No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	395/861	0.69 (0.57–0.84)
Age		
<65 yr	248/538	0.70 (0.54–0.90)
≥65 yr	147/323	0.63 (0.45–0.88)
Sex		
Male	287/628	0.77 (0.61–0.97)
Female	108/233	0.54 (0.37–0.81)
Region of enrollment		
North America	75/207	0.79 (0.50–1.25)
Western Europe	97/210	0.59 (0.39–0.89)
Rest of the world	223/444	0.71 (0.54–0.92)
IMDC risk category		
Favorable	90/269	0.81 (0.53–1.24)
Intermediate	232/484	0.70 (0.54–0.91)
Poor	73/108	0.58 (0.35–0.94)
Karnofsky performance-status score		
90 or 100	292/688	0.69 (0.54–0.87)
70 or 80	102/172	0.67 (0.45–1.00)
PD-L1 combined positive score		
<1	137/325	0.87 (0.62–1.23)
≥1	240/497	0.62 (0.47–0.80)
No. of organs with metastases		
1	75/210	0.54 (0.33–0.87)
≥2	317/646	0.73 (0.58–0.91)



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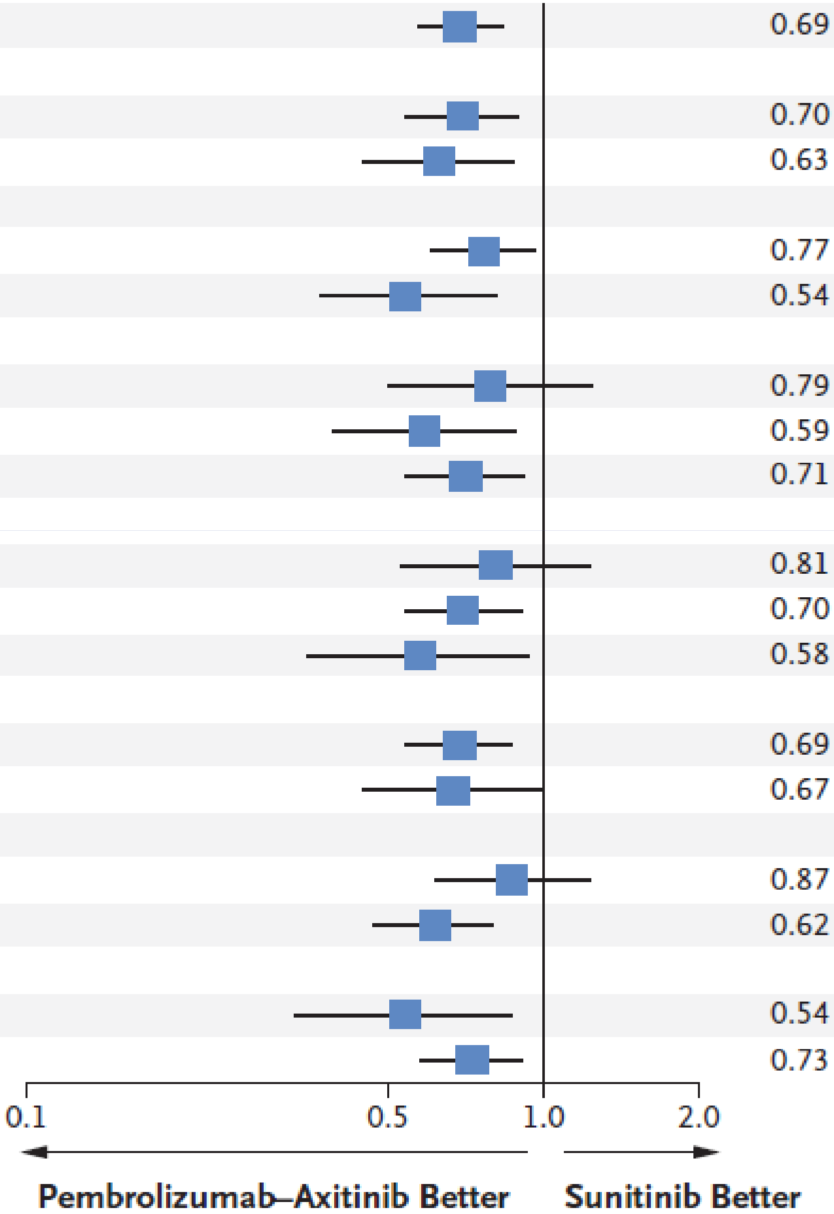


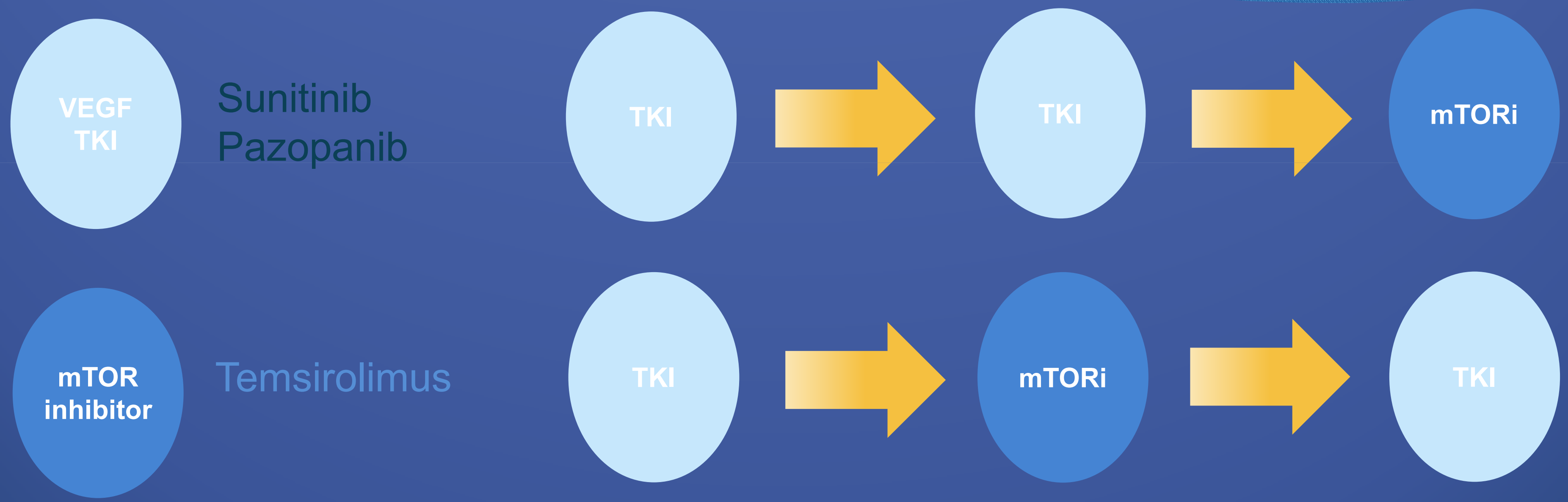
Table 2. Summary of Confirmed Objective Response.*

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+)

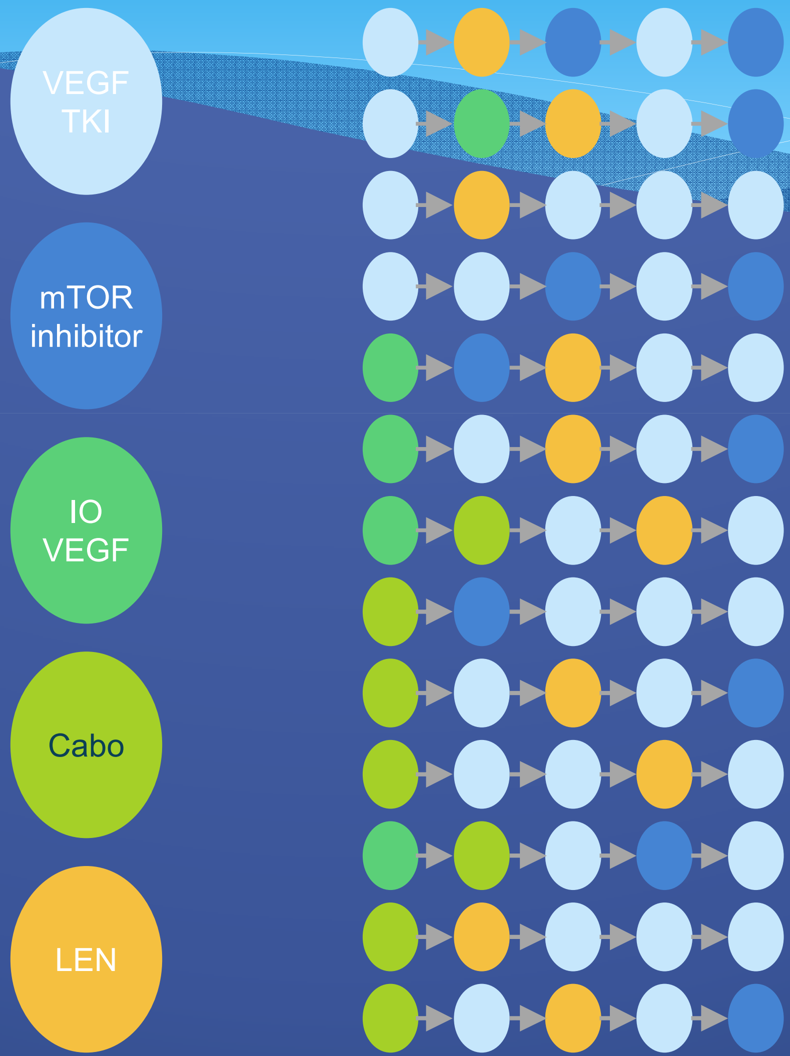
Table 3. Adverse Events of Any Cause That Occurred in 10% or More of Patients in the As-Treated Population.*

Event	Pembrolizumab–Axitinib (N=429)		Sunitinib (N=425)	
	Any Grade	Grade 3, 4, or 5†	Any Grade	Grade 3, 4, or 5‡
	number of patients (percent)			
Diarrhea	233 (54.3)	39 (9.1)	191 (44.9)	20 (4.7)
Hypertension	191 (44.5)	95 (22.1)	193 (45.4)	82 (19.3)
Fatigue	165 (38.5)	12 (2.8)	161 (37.9)	28 (6.6)
Hypothyroidism	152 (35.4)	1 (0.2)	134 (31.5)	1 (0.2)
Decreased appetite	127 (29.6)	12 (2.8)	125 (29.4)	3 (0.7)
Palmar–plantar erythrodysesthesia syndrome	120 (28.0)	22 (5.1)	170 (40.0)	16 (3.8)
Nausea	119 (27.7)	4 (0.9)	134 (31.5)	4 (0.9)
Alanine aminotransferase increased	115 (26.8)	57 (13.3)	64 (15.1)	13 (3.1)
Aspartate aminotransferase increased	112 (26.1)	30 (7.0)	69 (16.2)	10 (2.4)
Dysphonia	109 (25.4)	1 (0.2)	14 (3.3)	0
Cough	91 (21.2)	1 (0.2)	58 (13.6)	2 (0.5)
Constipation	89 (20.7)	0	62 (14.6)	1 (0.2)
Arthralgia	78 (18.2)	4 (0.9)	26 (6.1)	3 (0.7)
Weight decreased	76 (17.7)	13 (3.0)	47 (11.1)	1 (0.2)
Proteinuria	75 (17.5)	12 (2.8)	47 (11.1)	6 (1.4)
Dyspnea	69 (16.1)	7 (1.6)	46 (10.8)	5 (1.2)
Headache	68 (15.9)	4 (0.9)	69 (16.2)	2 (0.5)
Stomatitis	67 (15.6)	3 (0.7)	89 (20.9)	9 (2.1)
Asthenia	65 (15.2)	11 (2.6)	63 (14.8)	13 (3.1)
Pruritus	65 (15.2)	1 (0.2)	25 (5.9)	0
Vomiting	65 (15.2)	1 (0.2)	79 (18.6)	4 (0.9)
Rash	61 (14.2)	1 (0.2)	47 (11.1)	2 (0.5)
Back pain	57 (13.3)	4 (0.9)	43 (10.1)	7 (1.6)
Mucosal inflammation	57 (13.3)	4 (0.9)	93 (21.9)	8 (1.9)
Hyperthyroidism	55 (12.8)	5 (1.2)	16 (3.8)	0
Pyrexia	55 (12.8)	0	43 (10.1)	0
Pain in extremity	51 (11.9)	4 (0.9)	42 (9.9)	4 (0.9)
Abdominal pain	49 (11.4)	5 (1.2)	29 (6.8)	1 (0.2)
Blood creatinine increased	48 (11.2)	2 (0.5)	51 (12.0)	3 (0.7)
Dysgeusia	47 (11.0)	1 (0.2)	131 (30.8)	0
Anemia	34 (7.9)	3 (0.7)	100 (23.5)	21 (4.9)
Dyspepsia	22 (5.1)	0	62 (14.6)	1 (0.2)
Gastroesophageal reflux disease	18 (4.2)	0	48 (11.3)	3 (0.7)
Platelet count decreased	16 (3.7)	1 (0.2)	77 (18.1)	31 (7.3)
Thrombocytopenia	11 (2.6)	0	99 (23.3)	25 (5.9)
Neutropenia	8 (1.9)	1 (0.2)	82 (19.3)	28 (6.6)
Neutrophil count decreased	4 (0.9)	1 (0.2)	50 (11.8)	29 (6.8)
White-cell count decreased	2 (0.5)	0	43 (10.1)	12 (2.8)

Old paradigm
Sequencing approved agents



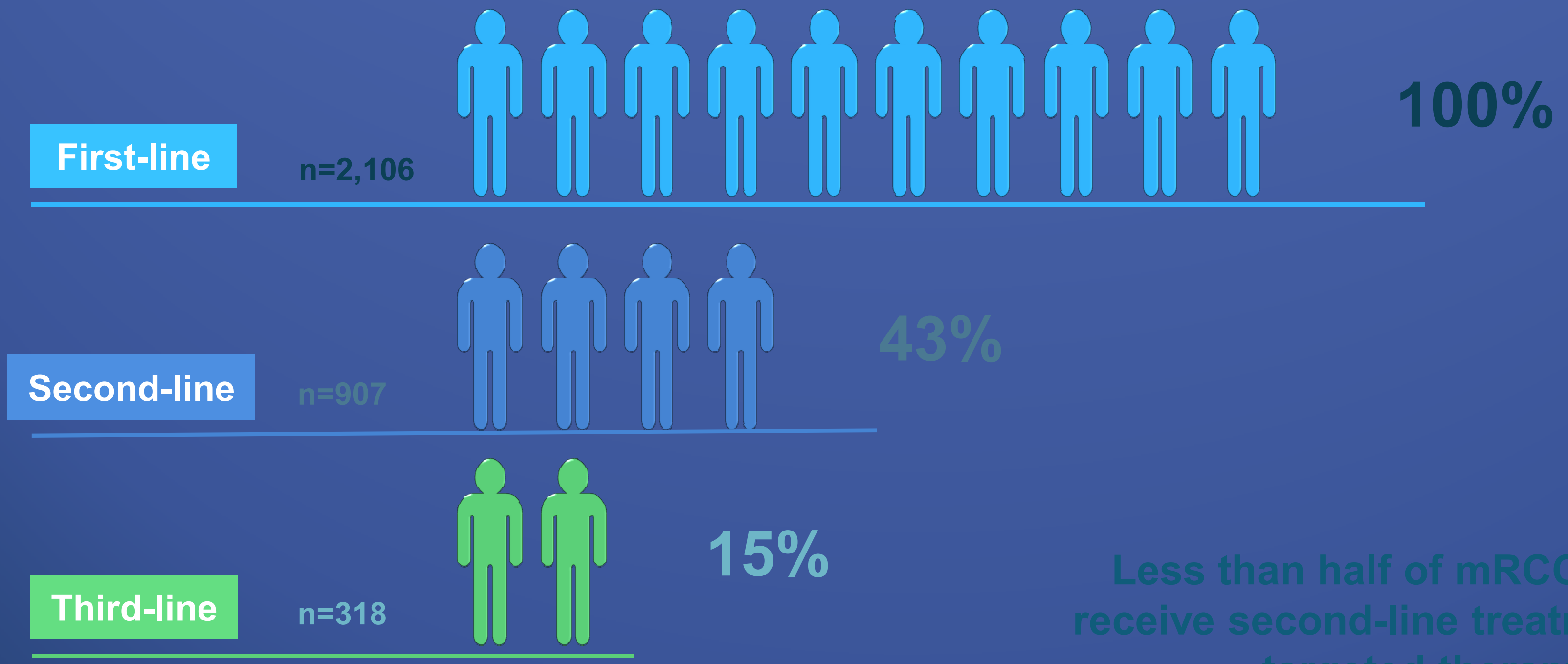
New paradigms: 2018



Modified from Hakimi A

How many patients reach second and third line?

Consecutive population-based patient samples were collected between 2005 and 2011 at 12 international cancer centers in Canada, USA, Singapore and Denmark. Patients with mRCC (n=2,106) were treated with targeted therapies as part of a clinical trial or as per the standard of care at the time. Median follow-up was 36 months.[1]



Less than half of mRCC patients receive second-line treatment with a targeted therapy[1]

1. Alimohamed N et al. Clin Genitourin Cancer 2013;12:e127-31