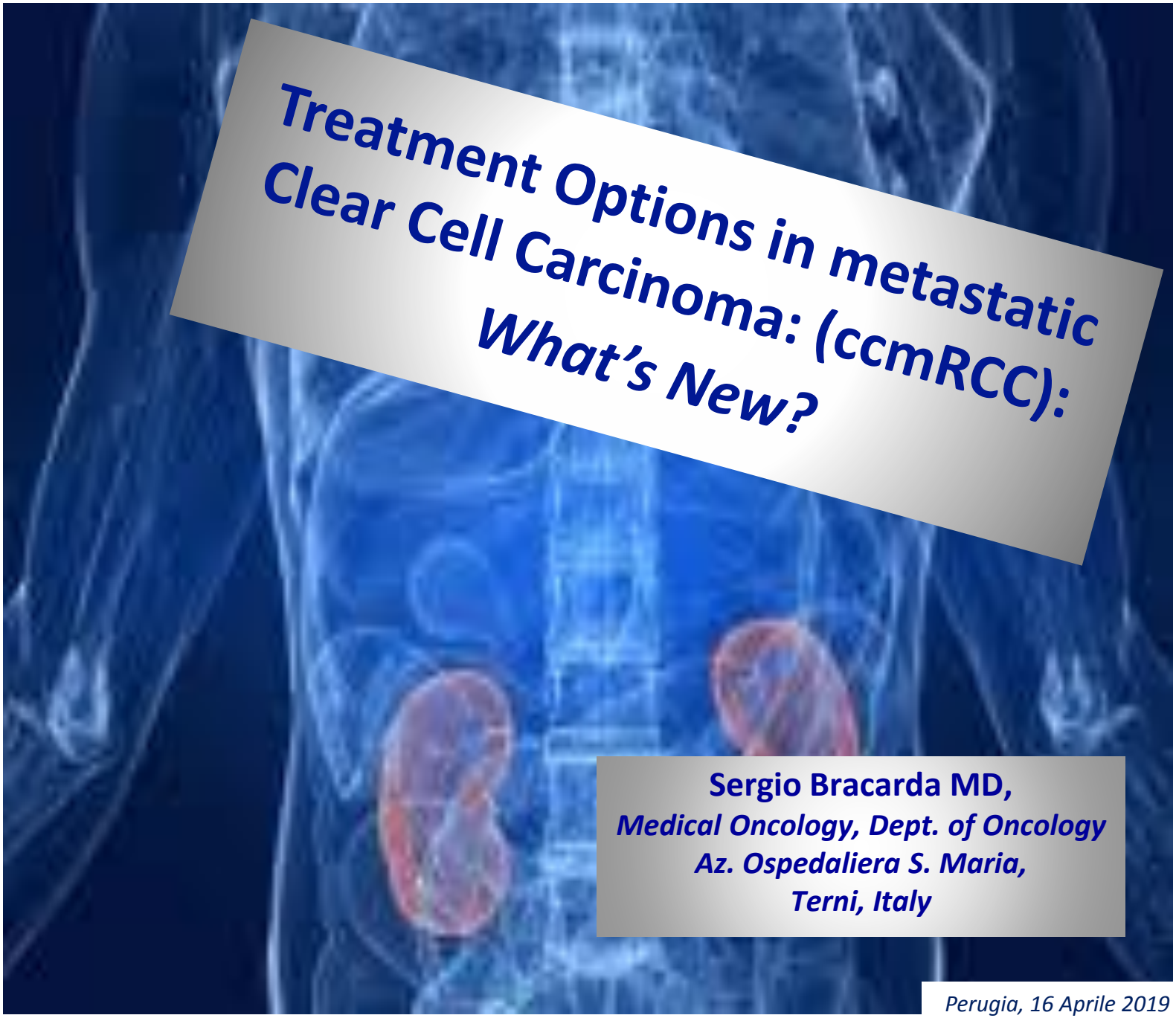


Treatment Options in metastatic Clear Cell Carcinoma: (ccmRCC): What's New?

Sergio Bracarda MD,
Medical Oncology, Dept. of Oncology
Az. Ospedaliera S. Maria,
Terni, Italy

Perugia, 16 Aprile 2019

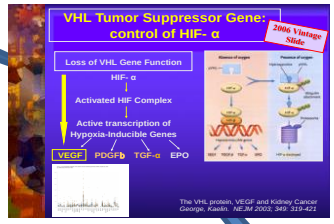
My Disclosures

- Adv. Board Member for: *Pfizer, BMS, Novartis, MSD, Roche, Astellas, Janssen, Ipsen.*
- Travel Accomodation with: *Pfizer, BMS, Roche, Astellas, Janssen, Ipsen. Bayer*
- Reasonable Honoraria (Talks) from: *Pfizer, Roche, Astellas, Novartis, BMS, Janssen*

Treatment Algorythm in RCC: A Continuosly Changing Scenario

10 Years ago: AntiAngiogenic Era (TKI, mTOR-I):

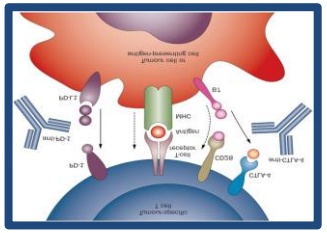
No more place for I-O



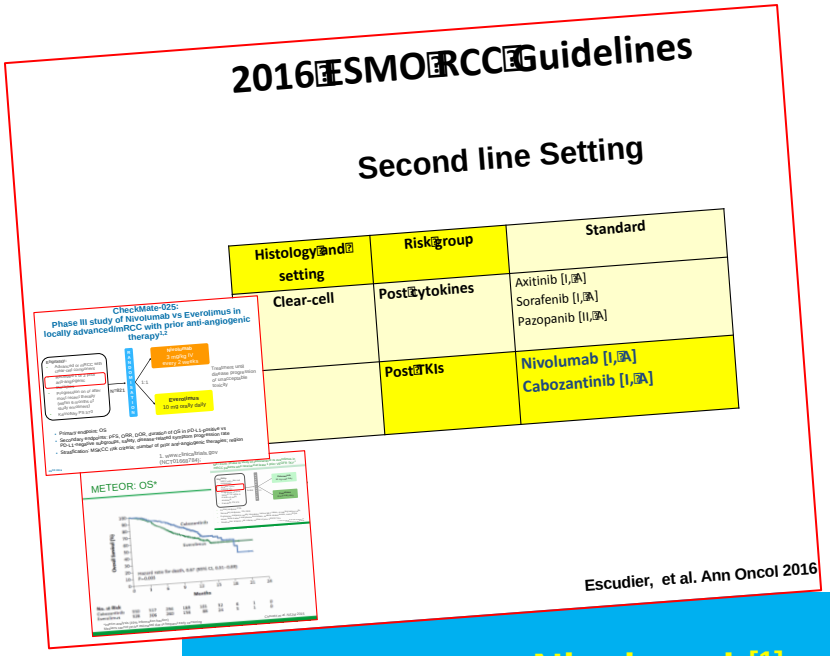
3 Years ago: going back to I-O Options (**Checkpoint Inh.**)

20 years ago: "Historical" I-O Agents: IFN & HD-IL2:

A Possibility for a Cure?



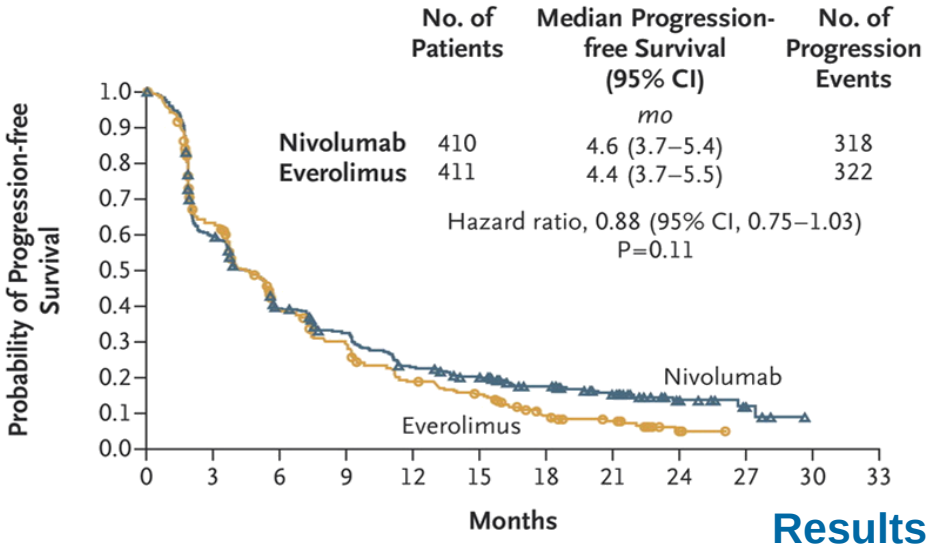
Second-line Treatment Options for mRCC: Summary of Efficacy

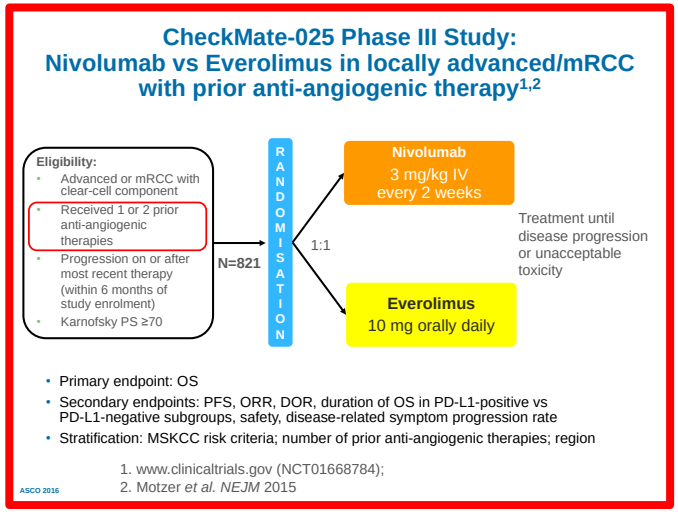


	Nivolumab[1]	Cabozantinib[2]	Axitinib [3,4]	Lenvatinib/ Everolimus[5,6]
Median PFS, *mos*	4.6	7.4	6.7	14.6
ORR, %	25	17	19	43
Median OS, mos	25.0	21.4	20.1	25.5

1. *Motzer RJ, et al. N Engl J Med. 2015;373:1803-1813.*
2. *Choueiri TK, et al. Lancet Oncol. 2016;17:917-927.*
3. *Rini BI, et al. Lancet. 2011;378:1931-1939. 4. Motzer RJ, et al. Lancet Oncol. 2013; 14:552-562.*
5. *Motzer RJ, et al. Lancet Oncol. 2015;16:1473-1482. 6. Hutson TE, et al. ASCO 2016. Abstract 4553.*

CheckMate-025: PFS & OS results



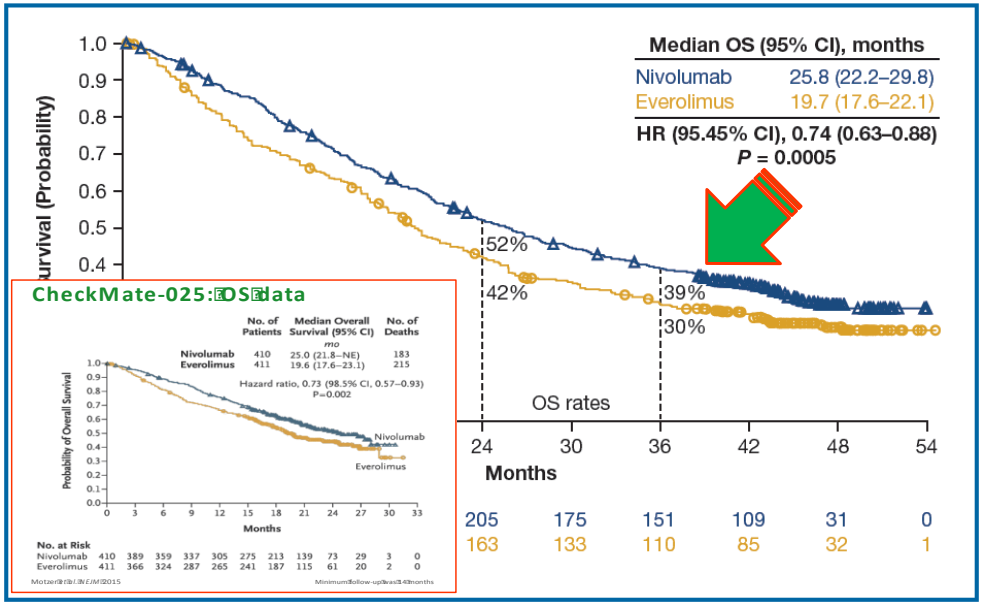


Results

CheckMate-025 Study. *Three-Year Efficacy Update*.

- Median OS remained significantly longer with Nivo vs Eve, with 3-yr OS rates of 39% vs 30%. (**Fig.1**)

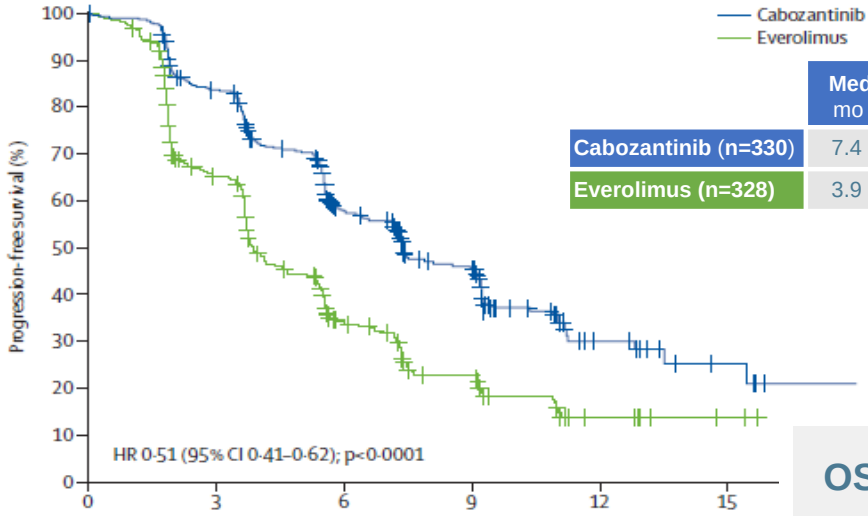
Figure 1. Overall survival



Motzer *et al. NEJM 2015*

Presented at the 16th International Kidney Cancer Symp.; November 3–4, 2017; Miami, FL, USA

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



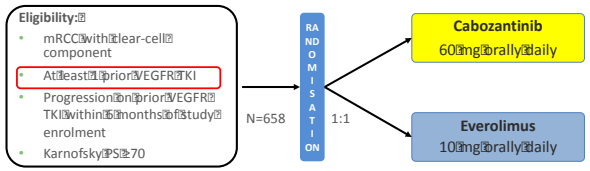
	Median PFS[1] mo (95% CI)	No. of events[1]
Cabozantinib (n=330)	7.4 (6.6–9.1)	180
Everolimus (n=328)	3.9 (3.7–5.1)	214

Number at risk						
Cabozantinib	330	261	148	88	20	6
Everolimus	328	174	72	37	10	2
Number censored						
Cabozantinib	0	17	37	32	47	12
Everolimus	0	51	24	13	16	8

Data cut-off: 22 May 2015

1. Choueiri

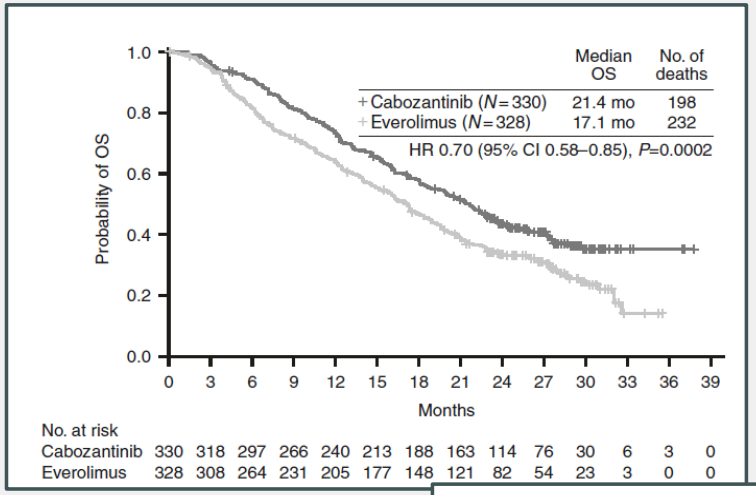
METEOR phase III Study:
Cabozantinib vs Everolimus in mRCC Pts who received at least 1 prior VEGFR TKI[1,2]



1. www.clinicaltrials.gov (NCT01865747);
2. Choueiri et al. *NEJM* 2015

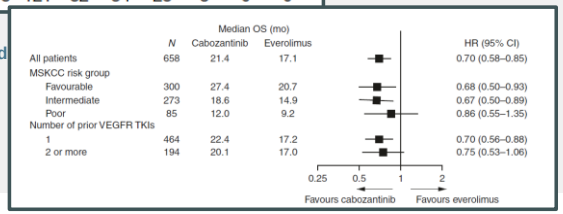
- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, ORR
- **Exploratory endpoints:** Safety, tolerability, tumour MET status, circulating tumour cells, serum bone markers and plasma biomarkers, skeletal-related events, and HRQoL
- **Stratification:** MSKCC risk criteria; number of prior VEGFR TKIs

OS in Meteor Study:
Extended Follow-Up



- Significant improvement in **OS** for cabozantinib compared with everolimus consistent with the earlier analysis.
- Nine additional months of follow-up

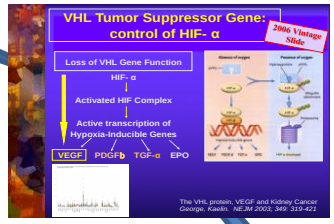
Overall survival through 2 October 2016. HR hazard ratio, OS overall survival



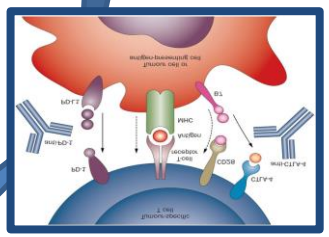
Long-term follow-up of overall survival for cabozantinib versus everolimus in advanced renal cell carcinoma
Robert J. Motzer, Bernard Escudier, Thomas Powles, Christian Scheffold and Toni K. Choueiri, British Journal of Cancer

Treating mRCC:
A Continuosly Changing Scenario

10 Years ago: AntiAngiogenic Era (*TKI, mTOR-I*):
No more place for I-O



3 Years ago: going back to I-O Options
(Checkpoint Inh.)



2 Years ago: going back to 1st Line I-O Options
(mainly Combo)

20 years ago: "Historical" I-O Agents: IFN & HD-IL2:
A Possibility for a Cure?

Is there a Way to Select the Most Appropriate 1st Line Treatment Option in mRCC ?

… Discussing …:

A) Patient' Factors
Performance status
Comorbidities

B) "Disease" ' Factors
Histology
Prognostic category

C) Treatment' Factors
Efficacy Data &
Tolerability Data

AZIENDA OSPEDALIERA SANTA MARIA TERNI

A) GOAL: An Inverse Toxicity-Related Algorithm for Daily Clinical Practice Decision Making in Advanced Kidney Cancer

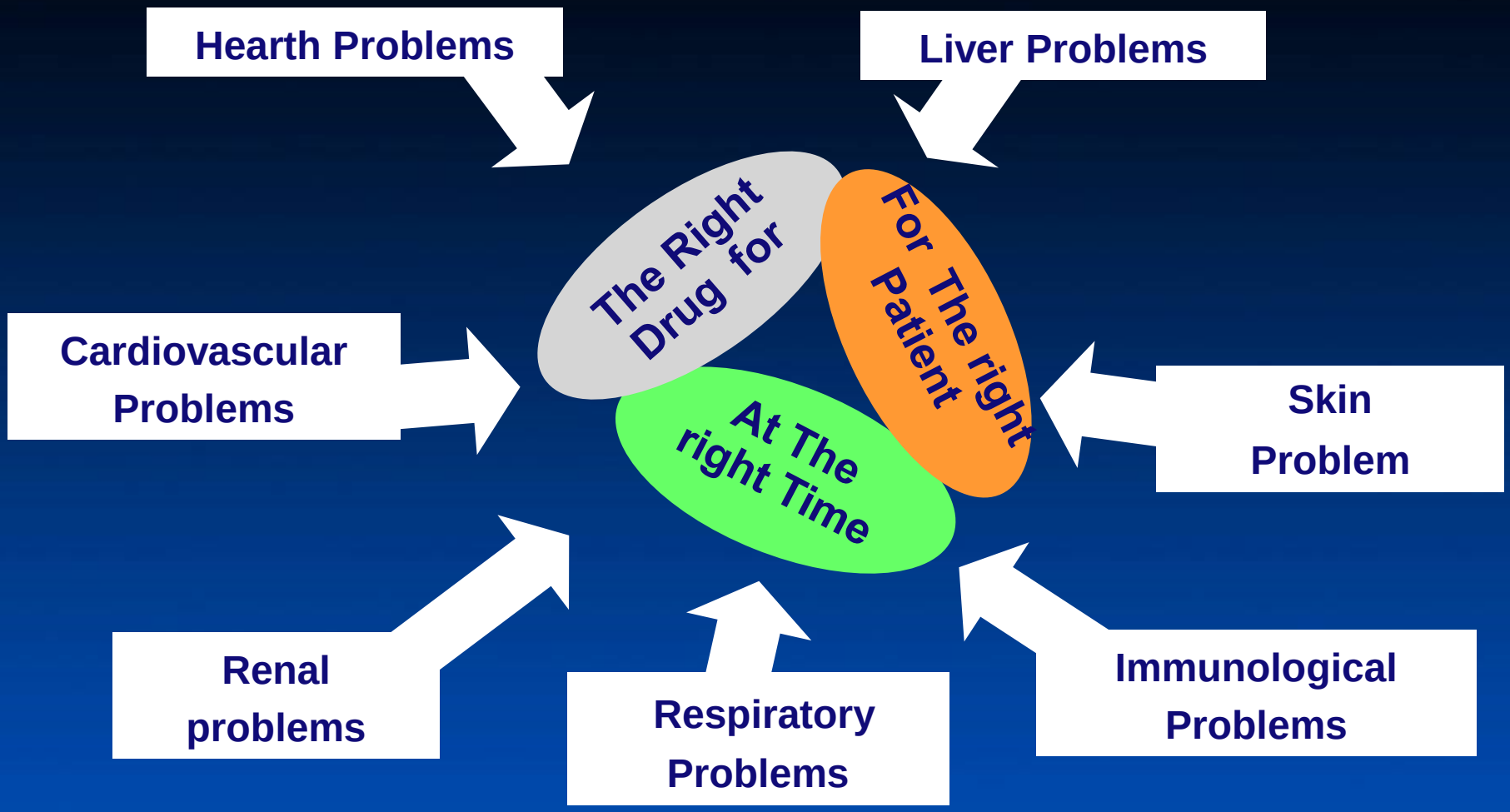
Eventual Comorbidity or relevant Clinical Condition	Potential Polarizing Toxicity	Drug to avoid in 1st line	Drug to avoid in 2nd line or later
Serious pre-existing cardiac problems	Seriuos cardiotoxicity	*SUNITINIB PAZOPANIB (?)*	*SUNITINIB*
Serious Liver impairment	Liver toxicity	*PAZOPANIB*	*SUNITINIB (?)*
Uncontrolled Hypertension	Hypertension	*SUNITINIB- BEVACIZUMAB+IFN*	*AXITINIB*
Uncontrolled Diabetes and dyslipedemia	Metabolic toxicities	-	*EVEROLIMUS*
Important Respiratory tract diseases (Eg COPD)	Pulmonary toxicity	-	*EVEROLIMUS*
Viral latent infections (e.g. active HBV, HCV infections)	Viral reactivation	-	*EVEROLIMUS*
Some Job Situations	Dermatological toxicity	*SORAFENIB*	*SORAFENIB*
History of Thromboembolisms or Haemorrages.	Vascular events -	*BEVACIZUMAB+ IFN*	-

AZIENDA OSPEDALIERA SANTA MARIA TERNI

Bracarda S. et al. Critical Reviews in Oncology/Hematology, 2014

A) Patient‘ Comorbidities, as a selection matter !

- one Patient, but more diseases -



Bracarda S. et al. Critical Reviews in Oncology/Hematology, 2014

B)

Prognostic Factor Classifications …
… From here to Eventual Predictive Factors ?

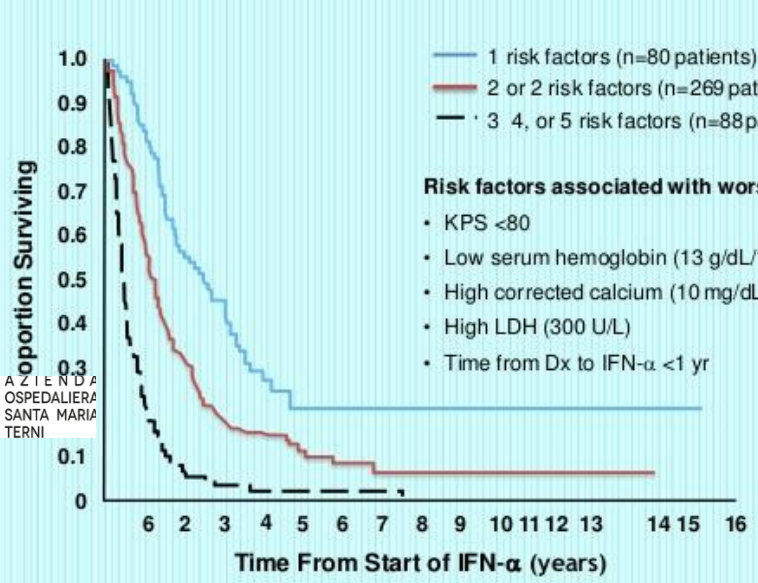
Bob's Data

Daniel's Data

Bob's (MSKCC) Risk Score

KPS	
Hb	
LDH	
Corrected sCalcium	
DFI	

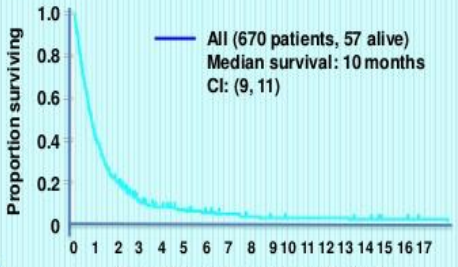
MSKCC Risk Factor Model in mRCC

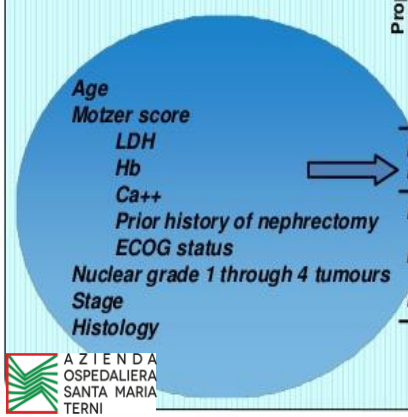


AZIENDA OSPEDALIERA SANTA MARIA TERNI

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

mRCC: prognostic factors





MSKCC risk group	Number of poor prognostic features	Patients (%)	Median OS (months)
Favourable	0	25	20
Intermediate	1–2	53	10
Poor	≥3	22	4

MSKCC risk factor model
Motzer RJ, et al J Clin Oncol 1999;17:2530–2540

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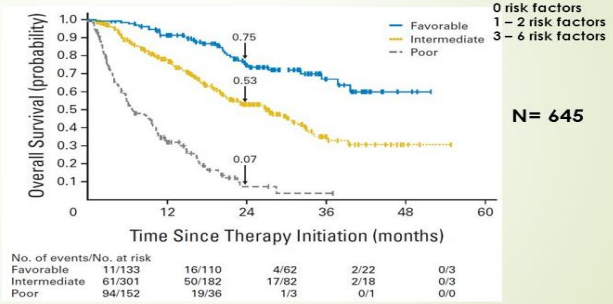
MSKCC Risk group	N° of Factors	Median OS
Good	0	19.9 months
Intermediate	1-2	10.3 months
Poor	3+	3.9 month

Prognosis

Daniel's (IMDC) Risk Score

KPS	< 80
Hb	< LLN
Platelet Count **Neutrophil Count**	> ULN > ULN
Corrected sCalcium	> 10mg/dl
Time from Diagnosis to Treatment	< 12m

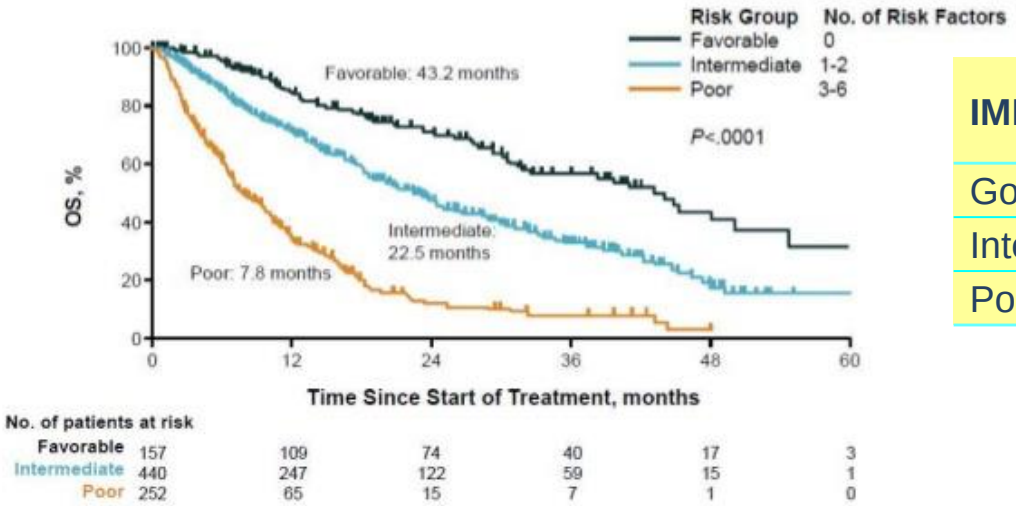
Prognostic Scores: Heng criteria (IMDC)



N= 645

Heng et al. J Clin Oncol. 2009

IMDC Prognostic Factors: Validated in First-Line Agents in mRCC



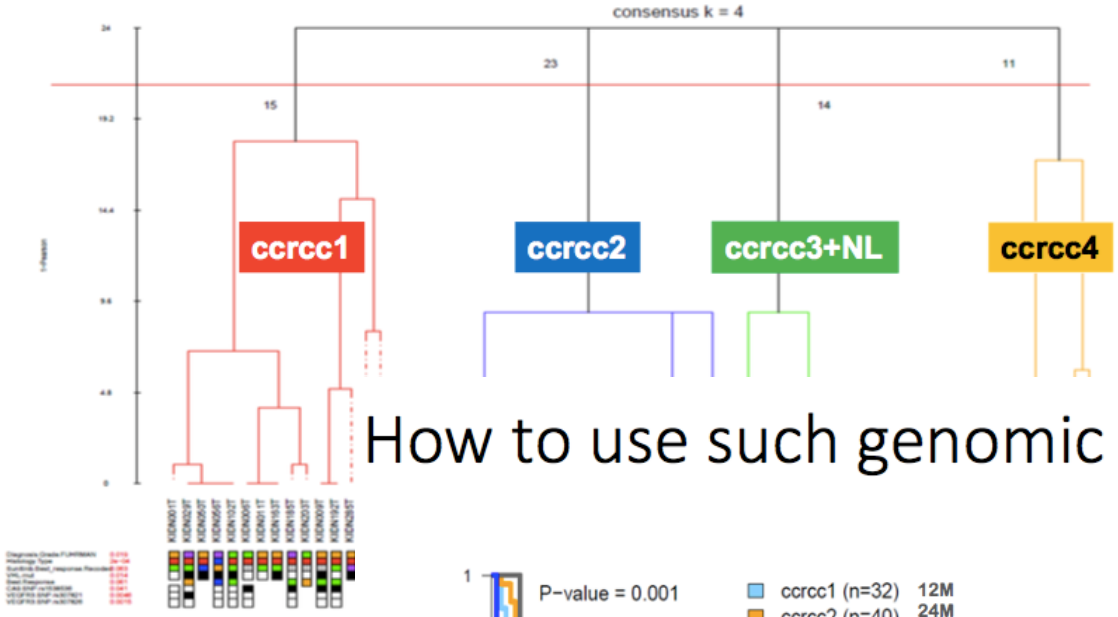
al. *Lancet Oncol.* 2013;14:141-148. Reproduced with permission of *Lancet Oncol.*

IMDC Risk group	N° of Factors	Median OS
Good	0	43.2 months
Intermediate	1-2	22.5 months
Poor	3-6	7.8 months

Prognosis

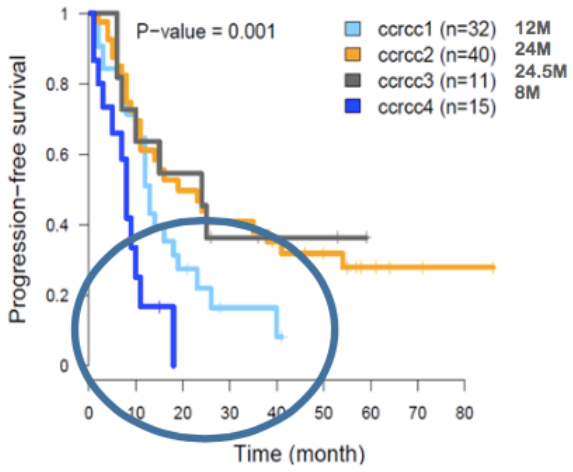
Any eventual available Predictive Classification ?

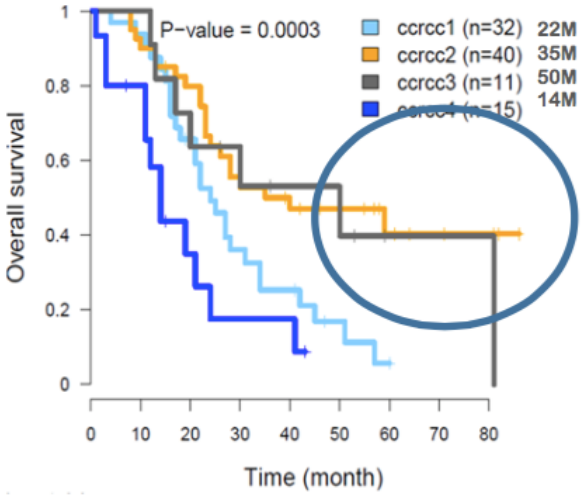
Genomic classification of RCC



Not validated !

How to use such genomic classification?





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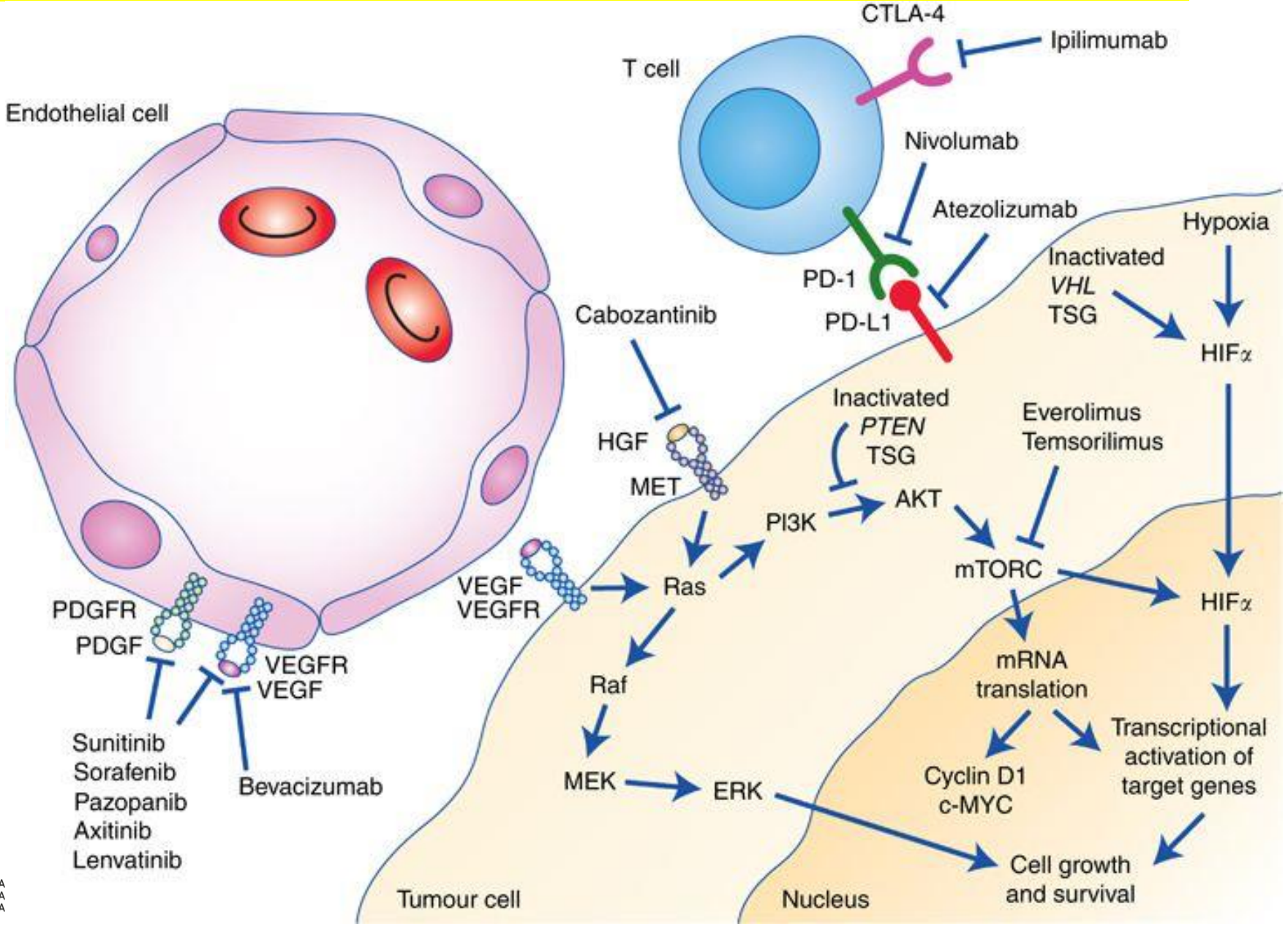
Beuselinck et al. Clin Cancer Res. 2015 Mar 15;21(6):1329-39.

C) Treatment' Factors *(Mechanism of Action and more)*



AZIENDA OSPEDALIERA SANTA MARIA TERNI

What We may use, at the moment, for a Daily Clinical Practice Decision Making?

… Some Informations from recent Trials on mRCC …

Is there a Way to select the most appropriate First Treatment Option in mRCC ?

…Discussing…:

A) Patient' Factors
Performance status
Comorbidities

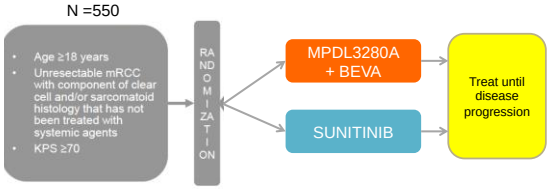
B) Disease' Factors
Histology
Prognostic category

C) Treatment' Factors
Efficacy Data &
Tolerability Data

AZIENDA OSPEDALIERA SANTA MARIA TERNI

IMmotion151

Randomized phase 3 study of Atezolizumab + Bevacizumab versus Sunitinib in patients with untreated mRCC

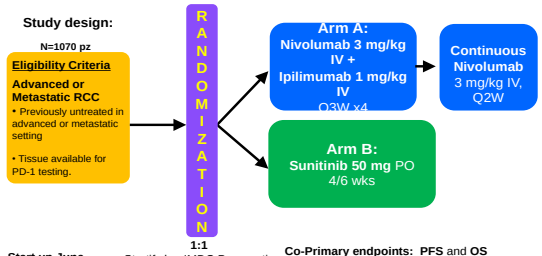


•Primary endpoint: PFS
•Secondary endpoints: OS, ORR, TTD, safety DoR

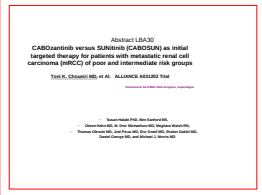
www. clinicaltrials.gov (NCT02420821))

CheckMate 214:

Randomized phase 3 study of Nivolumab + Ipilimumab vs Sunitinib in previously untreated mRCC



www. clinicaltrials.gov (NCT02231749)


Abstract LBA30
CABOzantinib versus SUNitinib (CABOSUN) as initial targeted therapy for patients with metastatic renal cell carcinoma (mRCC) of poor and intermediate risk groups
Toni K. Choueiri MD, et Al. ALLIANCE A031203 Trial

CABOzantinib versus SUNitinib (CABOSUN). ***ALLIANCE A031203 Trial***

Which place for TKIs ?

Advanced RCC (N=150)
- Clear cell component
- Measurable disease
- No prior systemic therapy
- ECOG PS 0-2
- IMDC intermediate or poor risk groups

Stratification:
- IMDC risk group: intermediate, poor
- Bone metastases: yes, no

Cabozantinib 60 mg qd orally (6 week cycles)

Randomization 1:1
No cross-over allowed

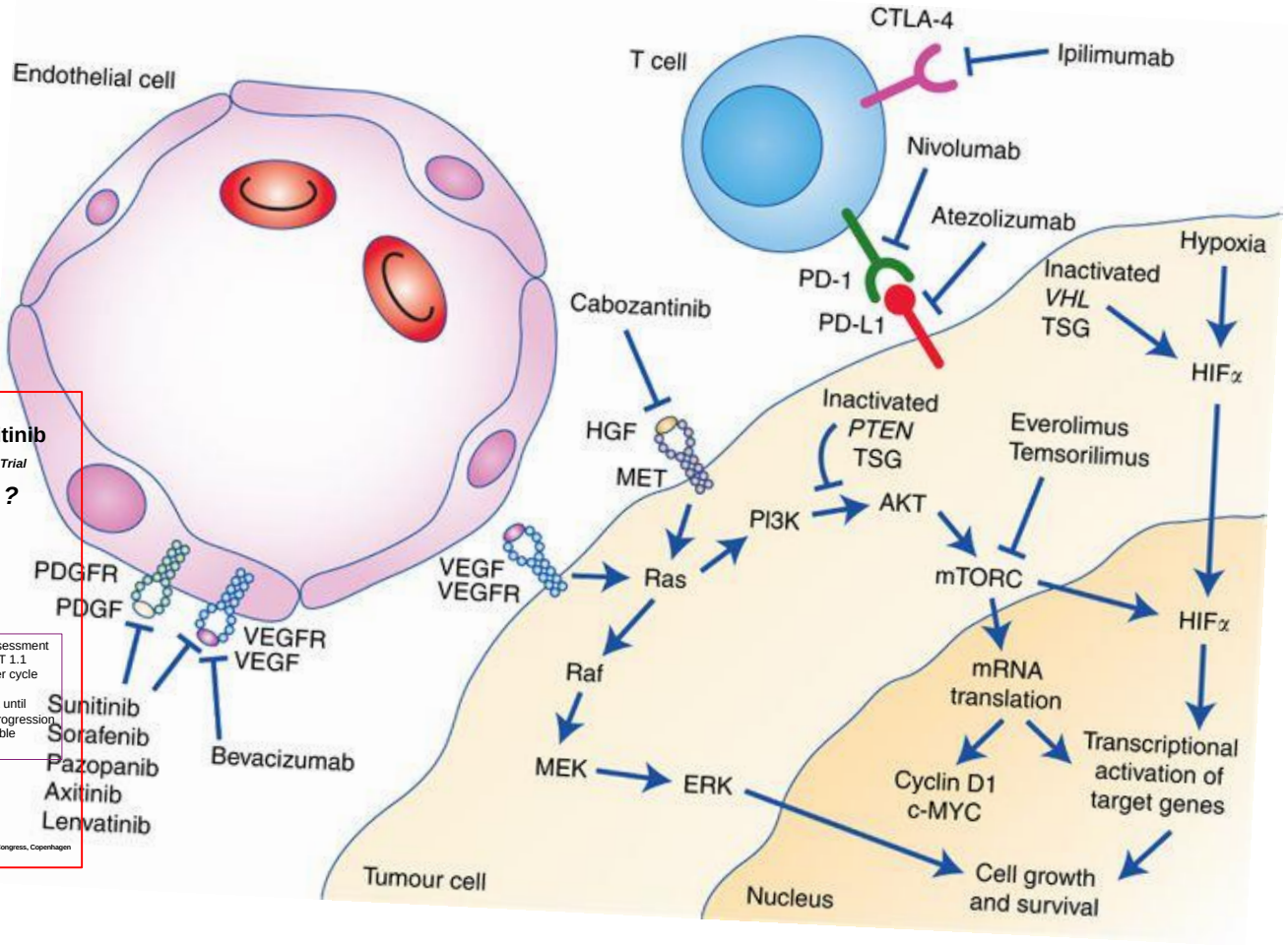
Sunitinib 50 mg qd orally (4 weeks on/2 weeks off)

Tumor assessment by RECIST 1.1 every other cycle

Treatment until disease progression or intolerable toxicity

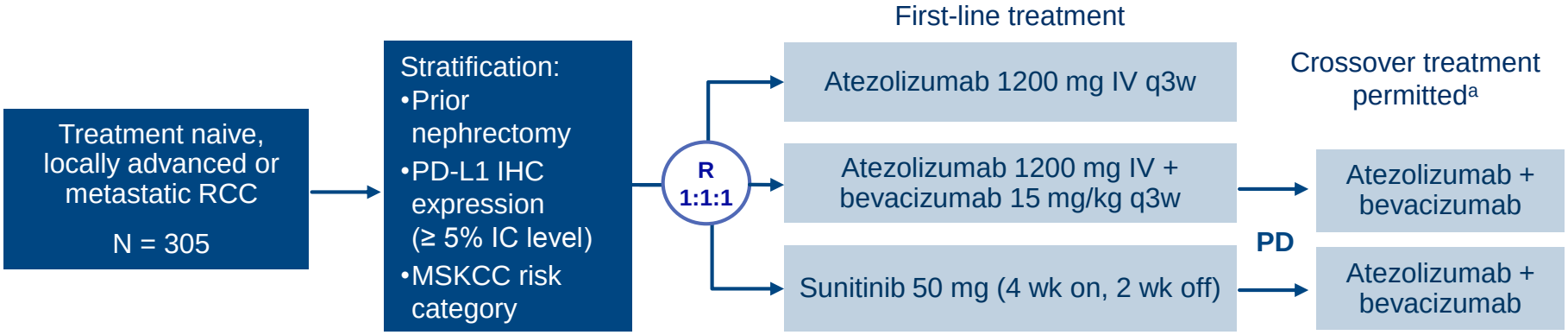
[1] Heng D et al., J Clin Oncol, 2009

Presented at the ESMO 2016 Congress, Copenhagen



AZIENDA OSPEDALIERA SANTA MARIA TERNI

IMmotion150 (*preliminary Ph.II Study to IMmotion 151*) Trial Design



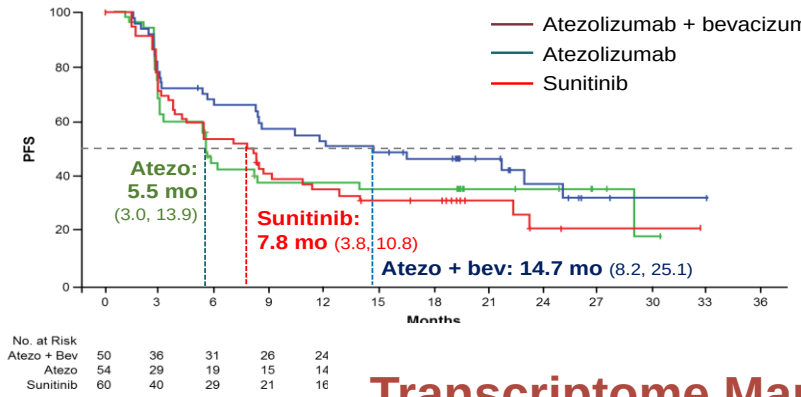
- ***Coprimary endpoints***: PFS (RECIST v1.1 by IRF) in ITT and PD-L1+ patients
- IMmotion150 designed to be hypothesis generating and inform the trial design of the Ph. III study IMmotion151
- ***Amendments included***: Based on Phase 1a data, the definition of PD-L1 positivity was revised from ≥ 5% to ≥ 1% of IC expressing PD-L1[1]
  - In addition to ITT patients, PD-L1+ patients were included in the co-primary EP of IRF-assessed PFS, after interim analyses

A Phase II Study of Atezolizumab With or Without Bevacizumab vs Sunitinib in Untreated Metastatic Renal Cell Carcinoma Patients

David McDermott,[1] Michael Atkins,[2] Robert Motzer,[3] Brian Rini,[4] Bernard Escudier,[5] Lawrence Fong,[6] Richard W. Joseph,[7] Sumanta Pal,[8] Mario Sznol,[9] John Hainsworth,[10] Walter M. Stadler,[11] Thomas Hutson,[12] Alain Ravaud,[13] Sergio Bracarda,[14] Cristina Suarez,[15] Toni Choueiri,[16] YounJeong Choi,[17] Mahrukh A. Huseni,[17] Gregg D. Fine,[17] Thomas Powles[18]

[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; [3]Memorial Sloan Kettering Cancer Center, New York, NY; [4]Cleveland Clinic, Cleveland, OH; [5]Gustave Roussy, Villejuif, France; [6]University of California, San Francisco School of Medicine, San Francisco, CA; [7]Mayo Clinic Hospital – Florida, Jacksonville, FL; [8]City of Hope Comprehensive Cancer Center, Duarte, CA; [9]Yale School Of Medicine, New Haven, CT; [10]Sarah Cannon Research Institute, Nashville, TN; [11]University of Chicago Medicine, Chicago, IL; [12]Texas Oncology - Baylor Charles A. Sammons Cancer Center, Dallas, TX; [13]CHU Hopitaux de Bordeaux - Hôpital Saint-André, Bordeaux, France; [14]Ospedale San Donato, Arezzo, Italy; [15]Vall d´Hebron Institute of Oncology, Vall d´Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; [16]Dana-Farber Cancer Institute, Boston, MA; [17]Genentech, Inc., South San Francisco, CA, USA; [18]Barts Cancer Institute, Queen Mary University of London, London, UK

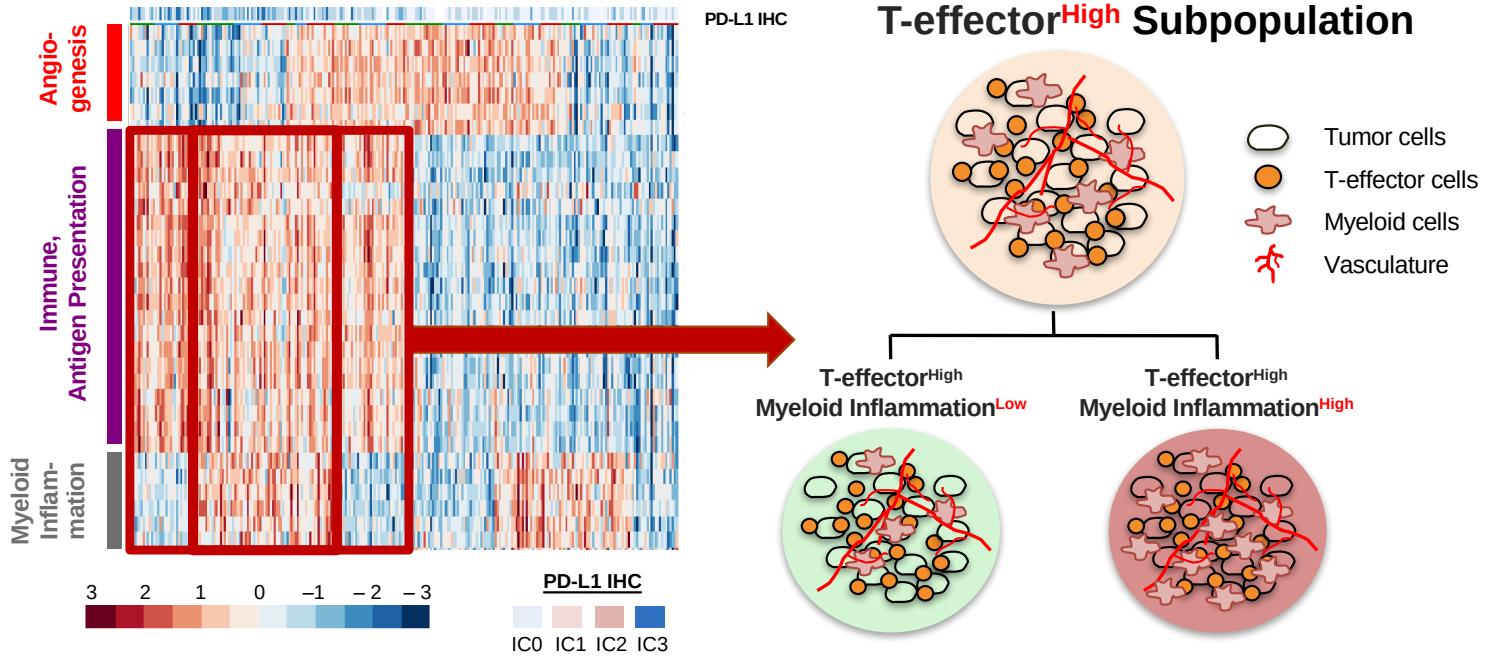
IMmotion150: IRF-Assessed PFS
≥ 1% of IC Expressing PD-L1



	Stratified HR (95% CI)	*P* Value[a]
Atezo + bev vs sunitinib	**0.64 (0.38, 1.08)**	0.095
Atezo vs sunitinib	**1.03 (0.63, 1.67)**	0.917

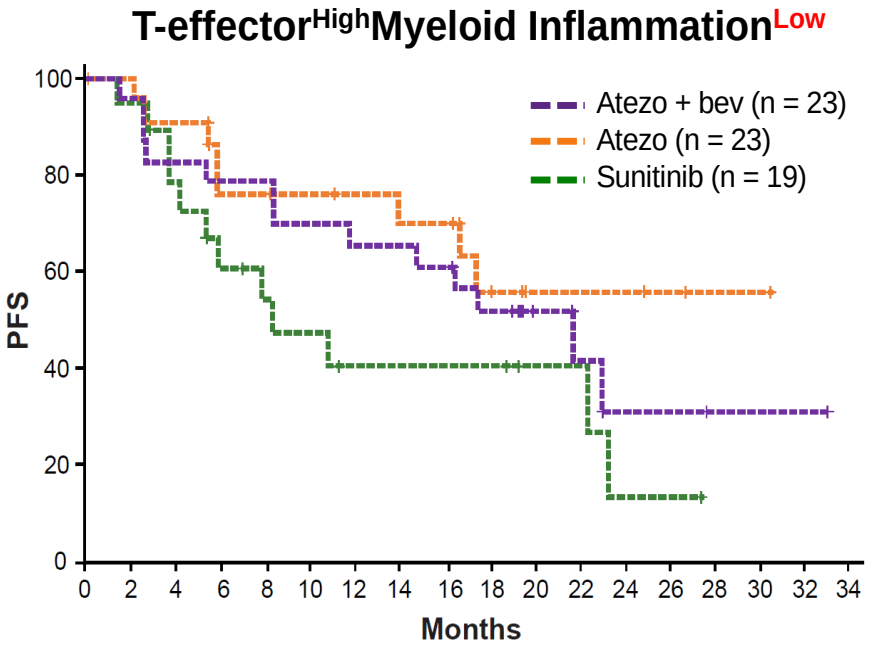
[a] *P* values are for descriptive purposes only and n

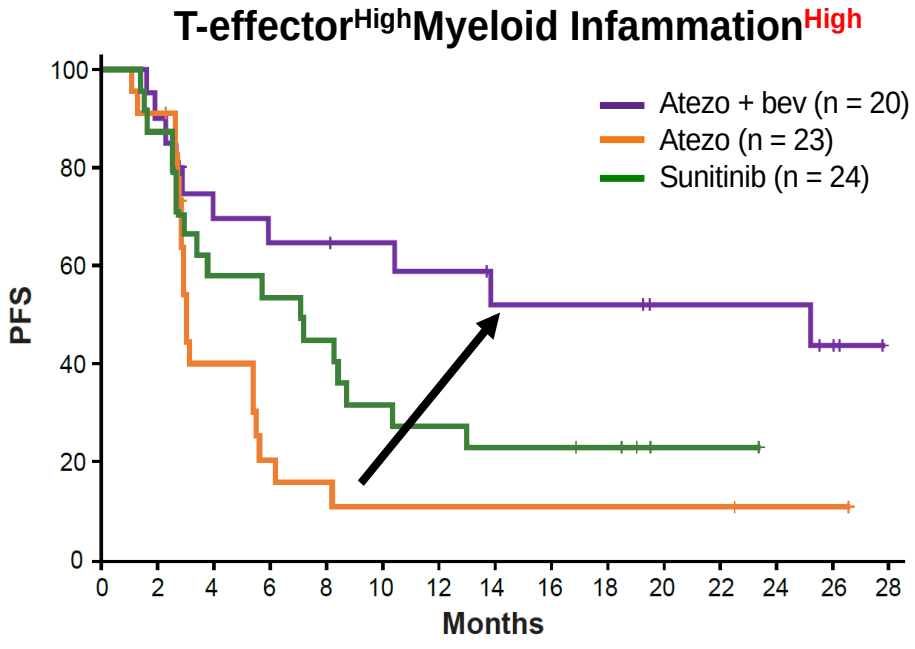
Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumors



Brauer, *Clin Cancer Res*. 2012; Herbst, *Nature* 2014; Powles, SITC 2015; Fehrenbacher, *Lancet* 2016. McDermott, AACR 2017.

Addition of Bevacizumab to Atezolizumab in 1L is Associated With Improved Benefit in T-effector^{High}/Myeloid Inflammation^{High} Subgroup



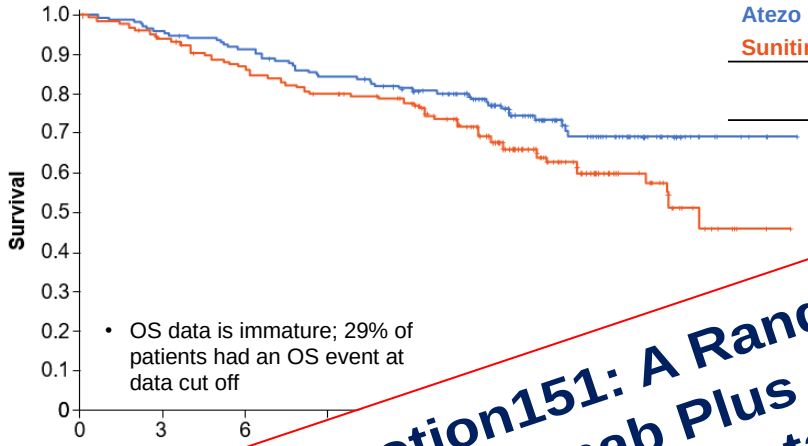


PFS measured by independent review facility.
T-effector Gene Signature: *CD8A, EOMES, PRF1, IFNG, CD274*.
High: ≥ median expression, Low: < median expression. McDermott, AACR 2017.

Overall Survival in PD-L1+

Secondary Endpoint

Median OS, months	
Atezo + Bev	Not reached
Sunitinib	23.3
HR, 0.68 (95% CI: 0.46, 1.00)	



- OS data is immature; 29% of patients had an OS event at data cut off

No. at Risk		
Atezo + Bev	178	169
Sunitinib	184	169

IMmotion151: A Randomized Phase III Study of Atezolizumab Plus Bevacizumab vs Sunitinib in Untreated Metastatic Renal Cell Carcinoma

Robert Motzer,[1] Thomas Powles,[2] Michael Atkins,[3] Bernard Escudier,[4] David McDermott,[5] Cristina Suarez,[6] Sergio Bracarda,[7] Walter Stadler,[8] Frede Donskov,[9] Jae Lyun Lee,[10] Robert Hawkins,[11] Alain Ravaud,[12] Boris Alekseev,[13] Michael Staehler,[14] Motohide Uemura,[15] Francis Donaldson,[16] Shi Li,[17] Mahrukh Huseni,[17] Christina Schiff,[17] Brian Rini[18]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Barts Health NHS Trust – St Bartholomew's Hospital, London, UK; [3]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; [4]Gustave Roussy, Villejuif, France; [5]Beth Israel Deaconess Medical Center, Boston, MA; [6]Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; [7]Ospedale San Donato, Arezzo, Italy; [8]The University of Chicago Medicine, Chicago, IL; [9]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; [10]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [11]The Christie NHS Foundation Trust, Manchester, UK; [12]CHU Hopitaux de Bordeaux – Hôpital Saint-André, Bordeaux, France; [13]P. Hertsen Moscow Oncology Research Institute, Moscow, Russia; [14]Klinikum der Universität München, Campus Großhadern, München, Germany; [15]Osaka University Graduate School of Medicine, Osaka, Japan; [16]Roche Products Ltd, Welwyn Garden City, UK; [17]Genentech, Inc., South San Francisco, CA; [18]Cleveland Clinic, Cleveland, OH

Study Design

Key Eligibility:
- Treatment-naïve advanced or metastatic RCC
- Clear cell and/or sarcomatoid histology
- KPS ≥ 70
- Tumor tissue available for PD-L1 staining

Stratification:
- MSKCC risk score
- Liver metastases
- PD-L1 IC IHC status (< 1% vs ≥ 1%)[a]

N = 915 → R 1:1

- Atezolizumab 1200 mg IV[b] + Bevacizumab 15 mg/kg q3w[b]
- Sunitinib 50 mg (4 wk on, 2 wk off)

IC, tumor-infiltrating immune cells. [a] Using SP142 IHC assay; [b] No dose reduction for atezolizumab or bevacizumab.

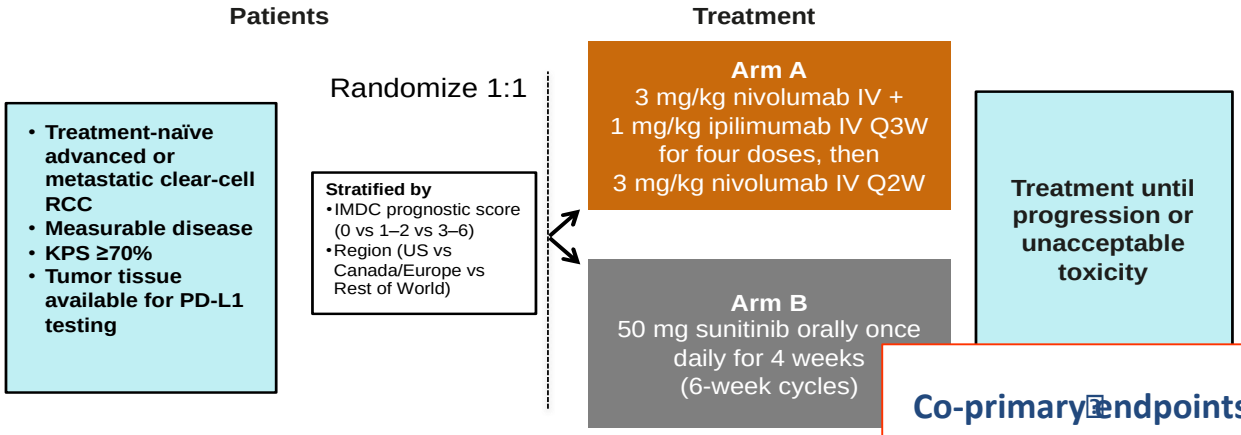
RCC

ORIGINAL ARTICLE FREE PREVIEW

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

Robert J. Motzer, M.D., Nizar M. Tannir, M.D., David F. McDermott, M.D., Osvaldo Arén Frontera, M.D., Bohuslav Melichar, M.D., Ph.D., Toni K. Choueiri, M.D., Elizabeth R. Plimack, M.D., Philippe Barthélémy, M.D., Ph.D., Camillo Porta, M.D., Saby George, M.D., Thomas Powles, M.D., Frede Donskov, M.D., Ph.D., et al., for the CheckMate 214 Investigators*

CheckMate 214: Study design



Co-primary endpoints

- In IMDC intermediate- and poor-risk patients
  - **ORR** (per independent radiology review committee, IRRC)
  - **PFS** (per IRRC)
  - **OS**

Secondary and exploratory endpoints

- Secondary endpoints (in intention-to-treat [ITT] patients)
  - ✓ ORR; PFS; OS
  - ✓ Adverse event incidence rate (in all treated patients)

PFS and OS secondary efficacy EPs were subject to hierarchical testing, first testing in intermediate/poor-risk patients followed by testing in ITT patients, if significant

- Exploratory endpoints
  - ✓ *ORR, PFS, and OS in favorable-risk patients;*
  - ✓ *Outcomes by tumor PD-L1 expr. level;*
  - ✓ *HRQoL based on NCCN FKSI-19 (Functional Assessment of Cancer Therapy-Kidney Symptom Index)*

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

AZIENDA OSPEDALIERA SANTA MARIA TERNI

The NEW ENGLAND JOURNAL of MEDICINE

Baseline characteristics

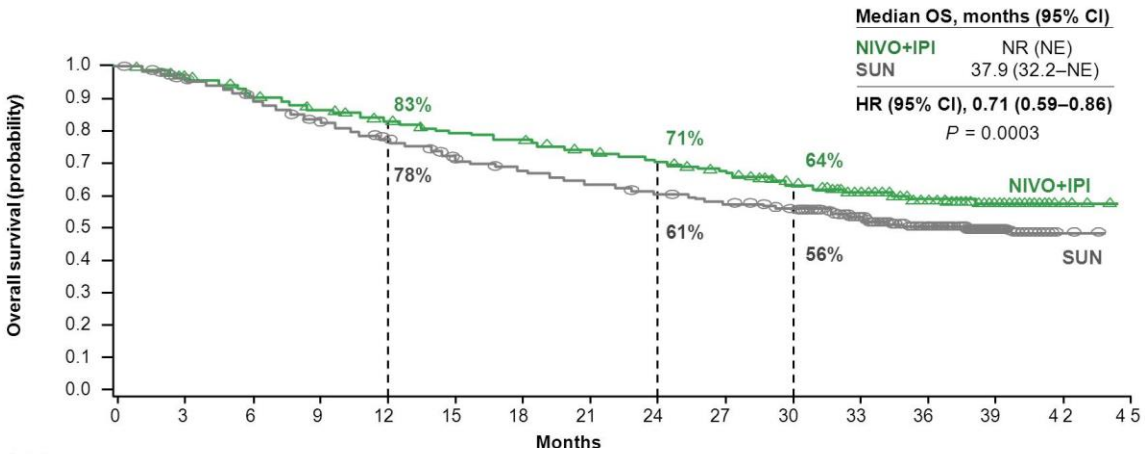
Characteristic	IMDC intermediate/poor risk		Intention to treat	
	NIVO + IPI N = 425	SUN N = 422	NIVO + IPI N = 550	SUN N = 546
Median age, years	62	61	62	62
Male, %	74	71	75	72
IMDC prognostic score (IVRS), %				
Favorable (0)	0	0	23	23
Intermediate (1–2)	79	79	61	61
Poor (3–6)	21	21	17	16
Region (IVRS), %				
USA	26	26	28	28
Canada/Europe	35	35	37	36
Rest of the world	39	39	35	36
Quantifiable tumor PD-L1 expression, %	n = 384	n = 392	n = 499	n = 503
<1%	74	71	77	75
≥1%	26	29	23	25

- Baseline characteristics in favorable-risk patients were similar, except tumor PD-L1 expression was lower than the intermediate/poor-risk patients and ITT population

CheckMate 214: 30m' OS OS

CheckMate 214

Overall Survival: ITT Patients



No. at risk

NIVO+IPI	550	523	492	464	443	425	4
SUN	546	507	472	435	404	367	3

CI, confidence interval; NE, not estimable; NR, not reached.

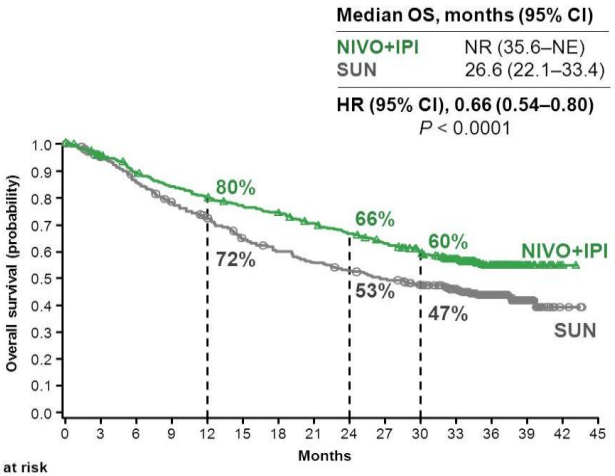
Presented By Nizar Tanni

CheckMate 214: 30m' OS OS

CheckMate 214

Overall Survival: by IMDC Risk

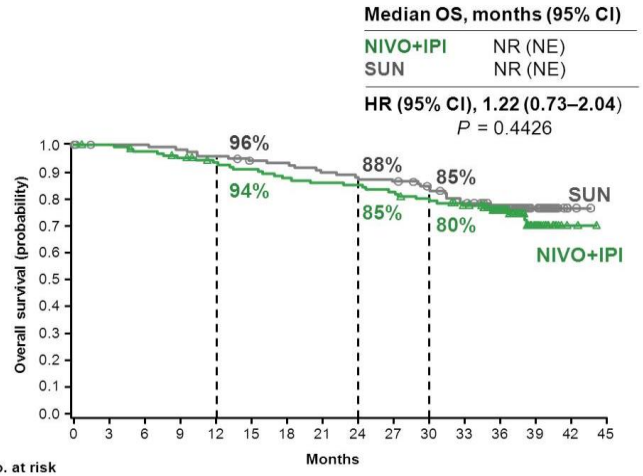
Intermediate/poor risk



No. at risk

NIVO+IPI	425	399	372	348	332	317	306	287	270	253	233	183	90	34	2	0
SUN	422	388	353	318	290	257	236	220	207	194	179	144	75	29	3	0

Favorable risk

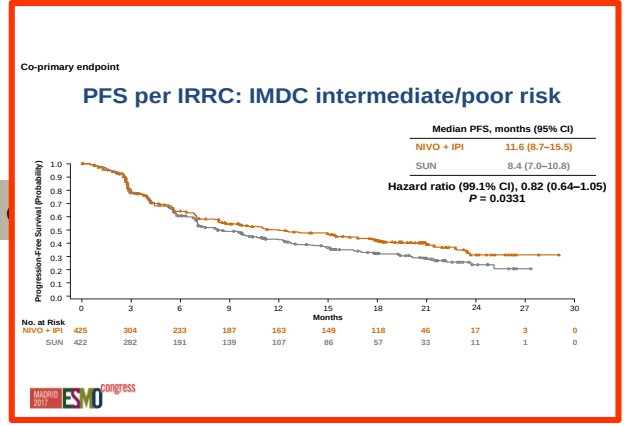


No. at risk

NIVO+IPI	125	124	120	116	111	108	104	102	101	98	94	88	71	24	2	0
SUN	124	119	119	117	114	110	109	105	103	101	96	88	70	26	2	0

Presented By Nizar Tannir at 2019 Genitourinary Cancers Symposium

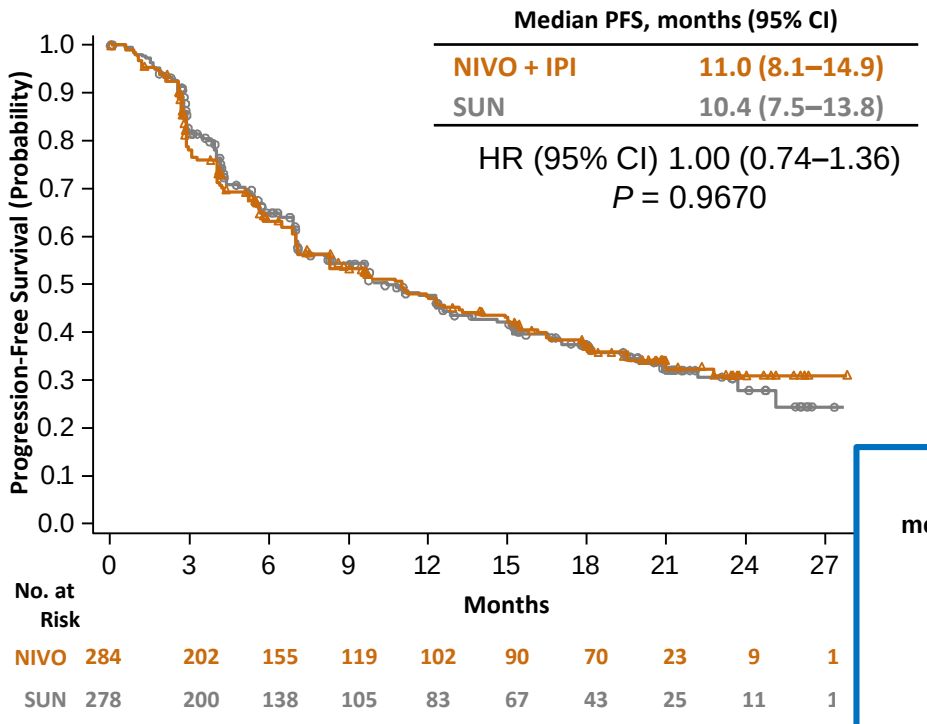
Exploratory



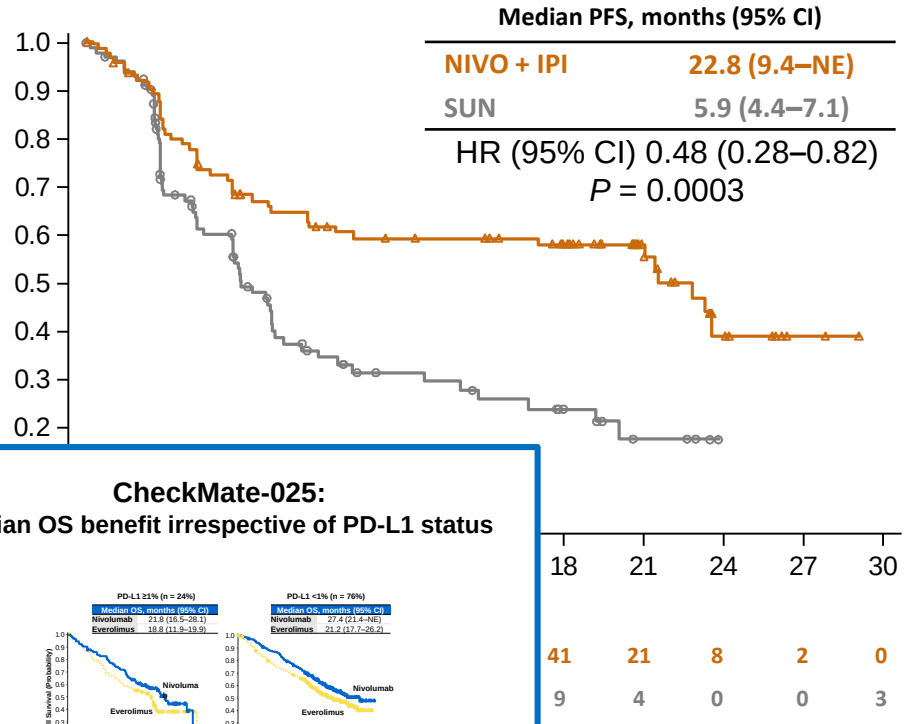
IMDC (intermediate/poor risk)

PFS by PD-L1 expression:

PD-L1 <1% (n = 562)



PD-L1 ≥1% (n = 214)



CheckMate-025:
median OS benefit irrespective of PD-L1 status

Adapted from Motzer et al, 2015, *N Engl J Med*.

MADRID AZIENDA OSPEDALIERA SANTA MARIA TERNI ESMO congress

Exploratory endpoint

CheckMate 214: PFS and ORR: IMDC favorable risk

IMDC Favorable Risk	N = 249[a]	
Outcome	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[b] % (95% CI)	**29 (21–38)**	**52 (43–61)**
	P = 0.0002	
PFS,[c] median (95% CI), months	**15.3** (9.7–20.3)	**25.1 (20.9–NE)**
	HR (99.1% CI) 2.18 (1.29–3.68) ***P* < 0.0001**	

[a]11% of patients in both arms had tumor PD-L1 expression ≥1%
[b]IRRC-assessed by RECIST v1.1
[c]IRRC-assessed

CheckMate 214: Antitumor activity by tumor PD-L1 expression level

Exploratory endpoint

	IMDC intermediate/poor risk				Intention to treat			
	PD-L1 <1%		PD-L1 ≥1%		PD-L1 <1%		PD-L1 ≥1%	
Outcome	NIVO + IPI N = 284	SUN N = 278	NIVO + IPI N = 100	SUN N = 114	NIVO + IPI N = 386	SUN N = 376	NIVO + IPI N = 113	SUN N = 127
ORR,[a] % (95% CI)	37 (32–43)	28 (23–34)	**58 (48–68)**	**22 (15–31)**	36 (31–41)	35 (31–40)	**53 (44–63)**	**22 (15–30)**
	P = 0.0252		*P* < 0.0001		*P* = 0.8799		*P* < 0.0001	
BOR,[a] %								
Complete response	7	1	16	1	9	2	14	1
Partial response	30	27	42	21	27	33	39	21
Stable disease	36	47	19	40	39	43	25	43
Progressive disease	20	13	14	25	18	11	14	23
NA	7	12	9	13	7	11	8	13

[a]IRRC-assessed

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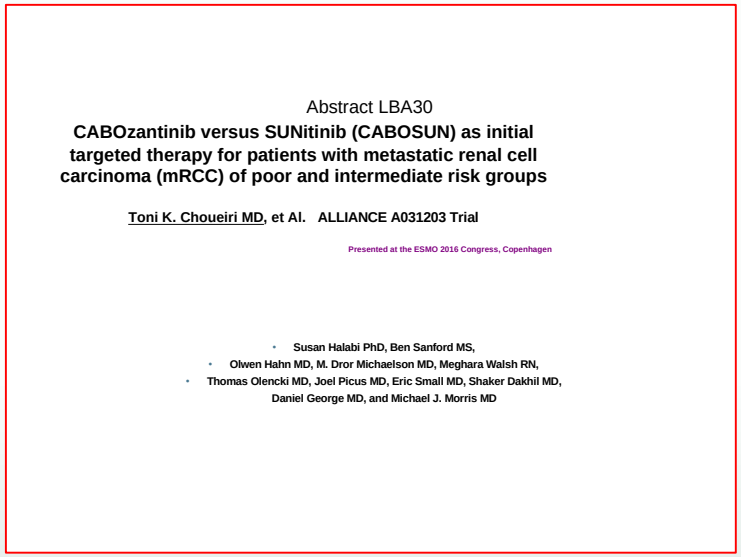

Abstract LBA30

CABOzantinib versus SUNitinib (CABOSUN) as initial targeted therapy for patients with metastatic renal cell carcinoma (mRCC) of poor and intermediate risk groups

Toni K. Choueiri MD, et Al. ALLIANCE A031203 Trial

Presented at the ESMO 2016 Congress, Copenhagen

- Susan Halabi PhD, Ben Sanford MS,
- Olwen Hahn MD, M. Dror Michaelson MD, Meghara Walsh RN,
- Thomas Olencki MD, Joel Picus MD, Eric Small MD, Shaker Dakhil MD, Daniel George MD, and Michael J. Morris MD

CABOzantinib versus SUNitinib (CABOSUN). *ALLIANCE A031203 Trial*

Which place for TKIs ?

Advanced RCC (N=150)
- Clear cell component
- Measurable disease
- No prior systemic therapy
- ECOG PS 0-2
- IMDC intermediate or poor risk groups

Cabozantinib
60 mg qd orally
(6 week cycles)

Randomization 1:1
No cross-over allowed

Sunitinib
50 mg qd orally
(4 weeks on/2 weeks off)

Tumor assessment by RECIST 1.1 every other cycle

Treatment until disease progression or intolerable toxicity

Stratification:
- IMDC risk group: intermediate, poor
- Bone metastases: yes, no

[1] Heng D et al., J Clin Oncol, 2009

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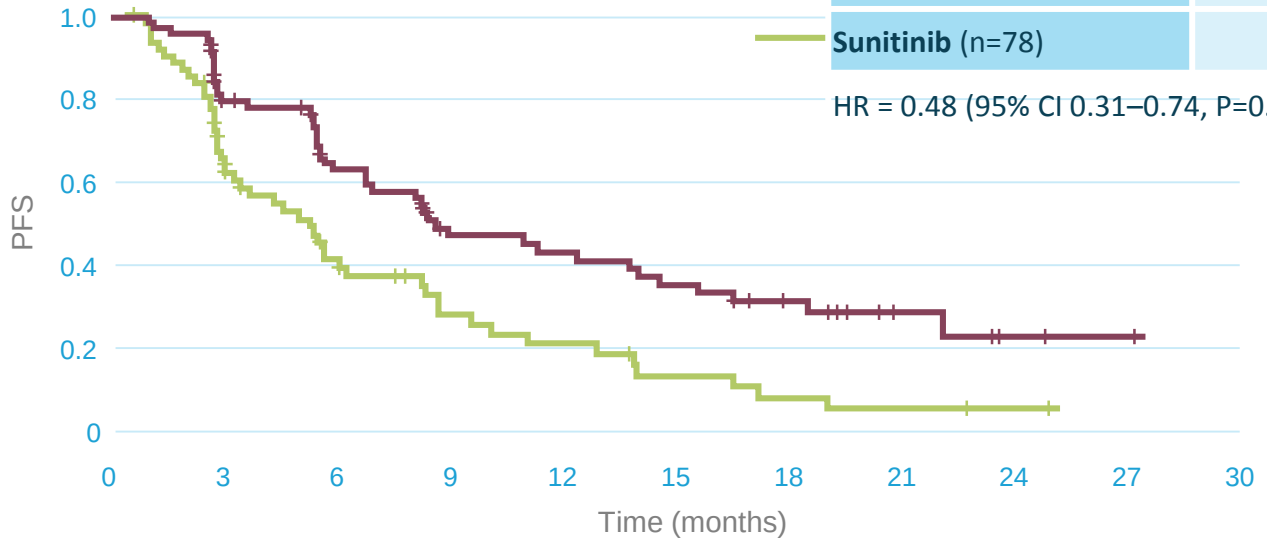
Phase 2 CABOSUN Study:
PFS by Independent Review Committee

Arm	mo (95% CI)
Cabozantinib (n=79)	**8.6** (6.8–14.0)
Sunitinib (n=78)	**5.3** (3.0– 8.2)

HR = 0.48 (95% CI 0.31–0.74, P=0.0008)



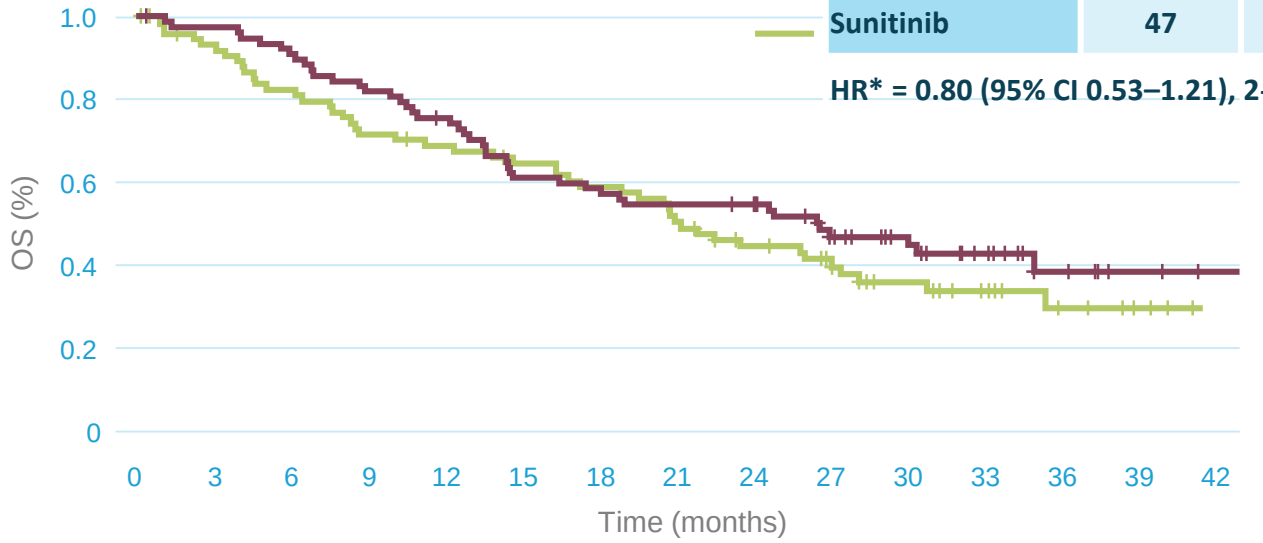
No. of patients at risk											
Cabozantinib	79	51	37	24	22	18	12	5	2	1	0
Sunitinib	78	36	21	12	9	5	3	2	1	0	0

Data cut-off: September 15, 2016 Choueiri TK, et al. ESMO 2017; abstract LBA38 and poster presentation

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

Arm	Deaths	
Cabozantinib	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



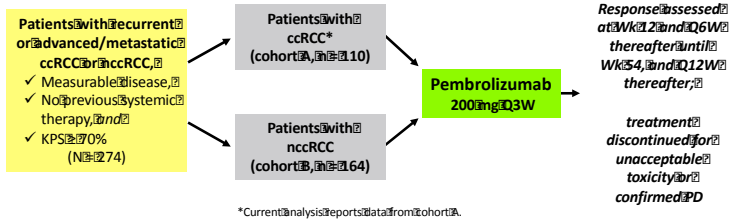
No. of patients at risk															
Cabozantinib	79	76	71	64	58	47	45	42	41	31	23	15	8	4	2
Sunitinib	78	69	61	53	50	46	42	36	29	24	17	12	6	3	0

Choueiri TK, et al. ESMO 2017; abstract LBA38 and poster presentation

KEYNOTE-427: *Clinical Response* (Primary Endpoint)

KEYNOTE-427 (*First-Line Mono Therapy with Pembro in mRCC*)

- First-Line, Single-arm, Open-label phase II study



*Current analysis reports data from cohort A.

- **Primary endpoint**: ORR per RECIST v1.1 criteria by blinded ICR
- **Secondary endpoints**: DoR, DCR, PFS, OS, safety, tolerability

McDermott DF, et al. ASCO 2018. Abstract 4500.

Response	Cohort A (n = 110)	
	n (%)	95% CI
ORR*	42 (38.2)	29.1-47.9
DCR (CR + PR + SD ≥ 6 mos)	**65 (59.1)**	**49.3-68.4**
Best overall response		
▪ **CR**	**3 (2.7)**	NR
▪ **PR**	**39 (35.5)**	
▪ **SD**	**35 (31.8)**	
▪ PD	31 (28.2)	
▪ No assessment	2 (1.8)	
Median follow-up, mos (range)	12.1 (2.5-16.8)	

*ORR confirmed by blinded ICR.

Response Cohort A (n = 110)	Cohort A (n = 110)				
	Favorable IMDC Risk (n = 41)	**Intermediate or Poor IMDC Risk (n = 69)**	**CPS ≥ 1 (n = 46)**	**CPS < 1 (n = 53)**	**Missing CPS Data (n = 11)**
Confirmed ORR, % (95% CI)	31.7 (18.1-48.1)	**42** (30.2-54.5)	**50.0** (34.9-65.1)	26.4 (15.3-40.3)	45.5 (16.7-76.6)
DCR,* % (95% CI)	65.9 (49.4-79.9)	**55.1** (42.6-67.1)	**67.4** (52-80.5)	49.1 (35.1-63.2)	72.7 (39-94)
Confirmed best overall response, %					
▪ **CR**	2.4	**2.9**	**6.5**	0	0
▪ **PR**	29.3	**39.1**	**43.5**	26.4	45.5
▪ SD	51.2	20.3	26.1	35.8	36.4
▪ PD	17.1	34.8	23.9	34.0	18.2
▪ No assessment	0	2.9	0	3.8	0

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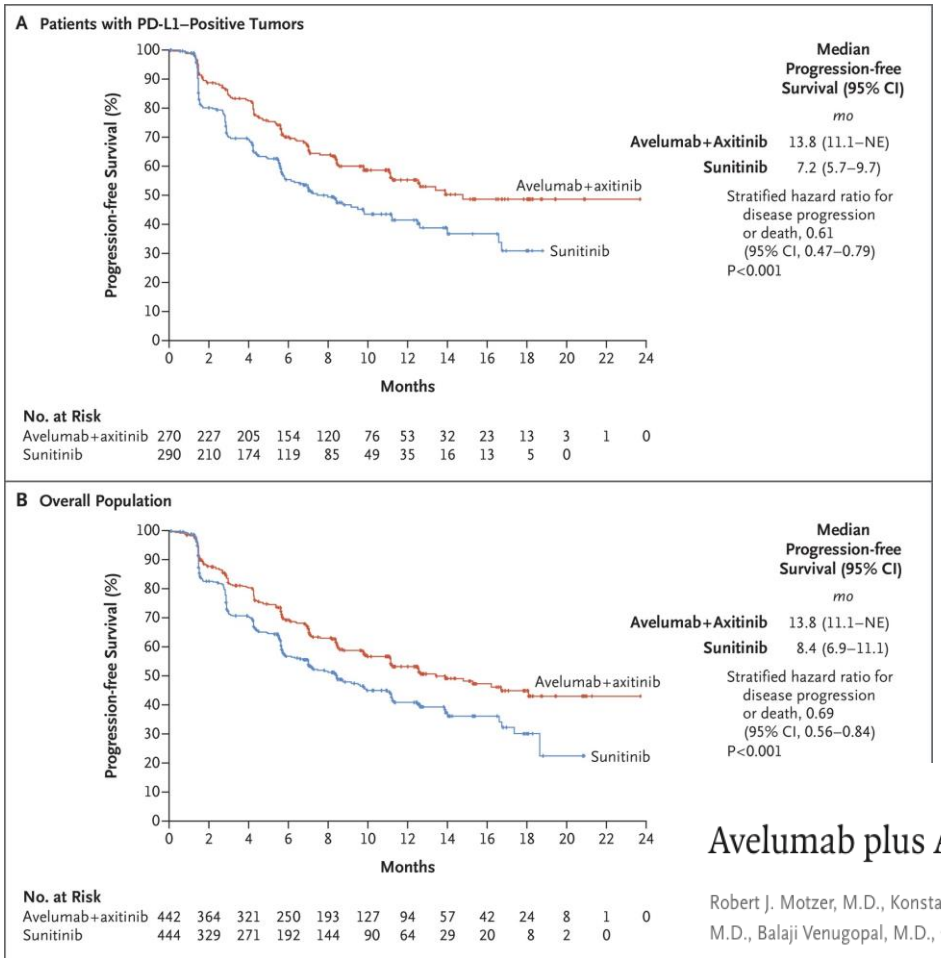
McDermott DF, et al. ASCO 2018. Abstract 4500.

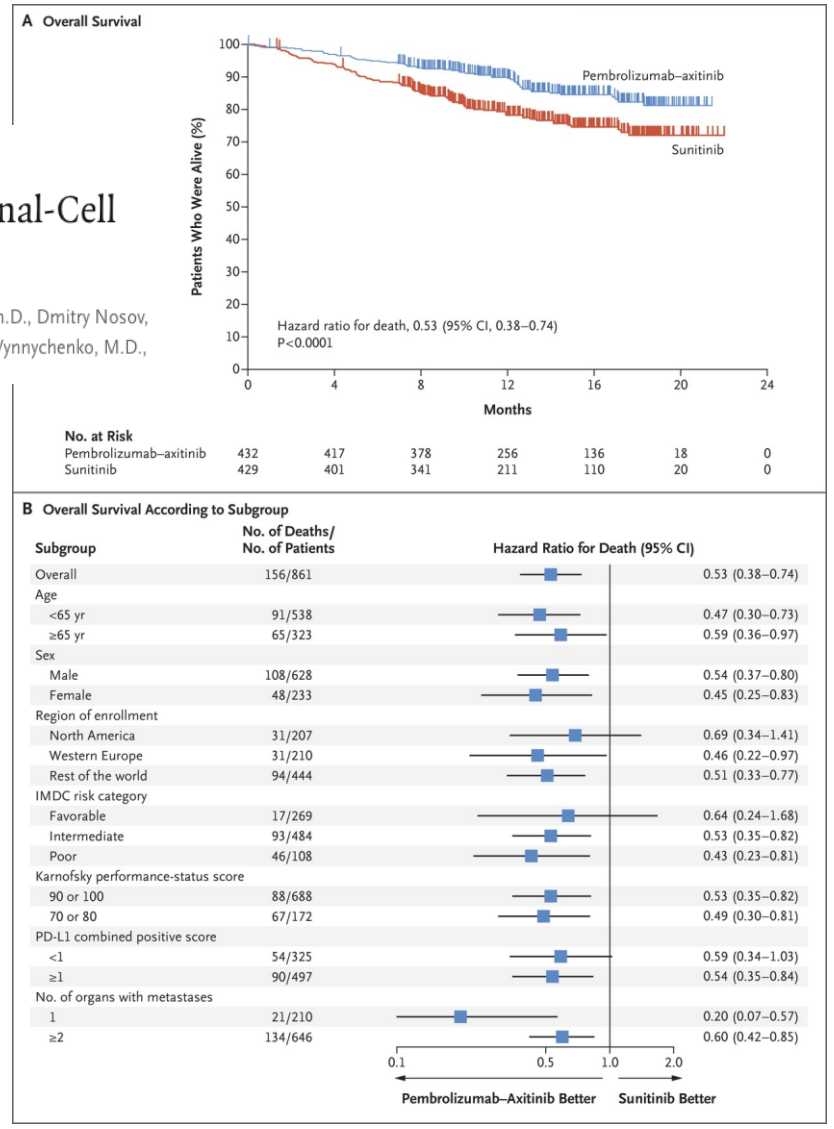
Finally, the Last Trials' Data

ORIGINAL ARTICLE FREE PREVIEW

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

Brian I. Rini, M.D., Elizabeth R. Plimack, M.D., Viktor Stus, M.D., Ph.D., Rustem Gafanov, M.D., Robert Hawkins, M.B., B.S., Ph.D., Dmitry Nosov, M.D., D.Sci., Frédéric Pouliot, M.D., Ph.D., Boris Alekseev, M.D., Denis Soulières, M.D., Bohuslav Melichar, M.D., Ph.D., Ihor Vynnychenko, M.D., Ph.D., Anna Kryzhanivska, M.D., et al., for the KEYNOTE-426 Investigators*





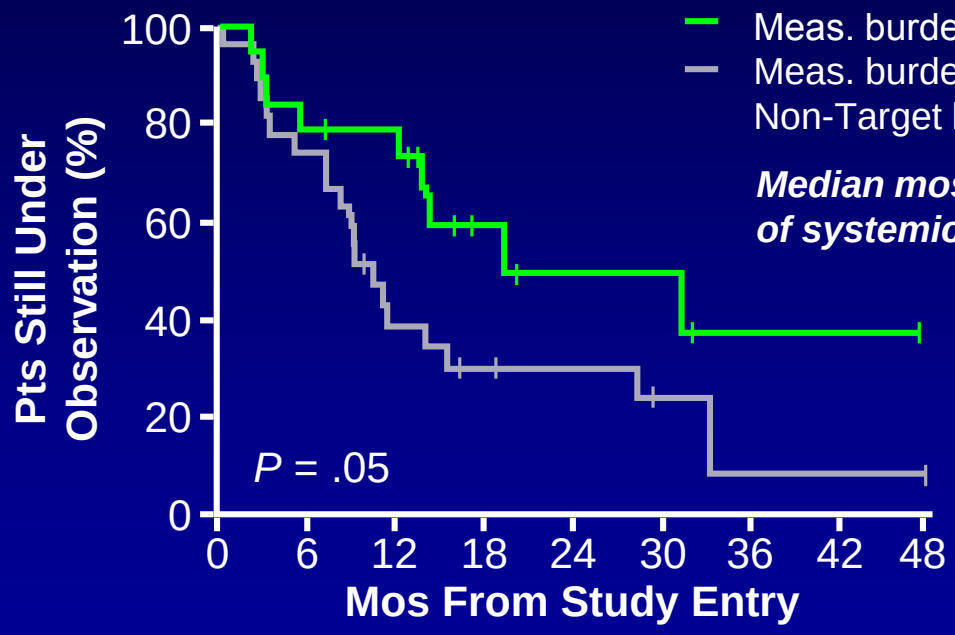
ORIGINAL ARTICLE FREE PREVIEW

Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

Robert J. Motzer, M.D., Konstantin Penkov, M.D., Ph.D., John Haanen, Ph.D., Brian Rini, M.D., Laurence Albiges, M.D., Ph.D., Matthew T. Campbell, M.D., Balaji Venugopal, M.D., Christian Kollmannsberger, M.D., Sylvie Negrier, M.D., Ph.D., Motohide Uemura, M.D., Ph.D., Jae L. Lee, M.D., Ph.D., Aleksandr Vasiliev, M.D., et al.

But, please consider also a possible Observational Phase, *before* starting Rx in some Cases

- Phase II study of pts with **mRCC** and no previous systemic therapy
  - Observation with periodic CT assessment; initiation of systemic treatment per discretion of physician and pt



  - Unaffected by IMDC risk group (*P* = .57), location or number of metastases

Rini B, et al. ASCO 2014. Abstract 4520.

Decision Making in mRCC: Conclusions

Advanced RCC: strongly interested from ***modern ImmunoTherapy Data***, ***but*** **TKIs** & **Rx Sequencing** remain important decision making Tools (*and changing the 1° Line and the available Biologic Data ……*)

1st Line Options, at the moment:

- ✓ **(IMDC Int/poor Risk):** Moving to **Ipi+Nivo** because of the >**OS**, with **Cabo** (significantly improving PFS) *and* ***Axi+Pembro*** *as possible further Options.*
- ✓ **(IMDC Good Risk):** ***Suni*** *(Pazo & Tivo?) remain the treatment of Choice, … with* ***Ipi+Nivo***, ***Axi+Pembro***, ***Beva+Atezo*** *or* ***Pembro Alone*** *as possible further options.*

2nd Line (Standards of Care) **Options:**

- ✓ **Nivo** & **Cabo** (but changing the 1° Line ….). But, some well identified Pts may be also treated with **Axi** (after **Suni…**).

3rd Line Options:

- ✓ To be considered (..Cabo/Eve, ?), in Pts with a favourable History.

Thanks !

AZIENDA OSPEDALIERA SANTA MARIA TERNI