What's new in RCC and implications for patients in Canada

Canadian Urological Association
The Voice of Urology in Canada

Association des urologues du Canada
La voix de l'urologie au Canada

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Faculty Disclosures

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Grants/honorarium: Astellas, Amgen, Bayer, Janssen
Clinical trials: Astellas, AstraZeneca, Bayer, BMS, Clovis, Janssen, Roche

Learning Objectives

By the end of this session, participants will:

- Review key scientific & clinical data from ESMO and implications for management of RCC in Canada
- Discuss new HC approvals and implications for management of advanced RCC
- Debate optimal RCC treatment sequence in light of new data and recent HC approvals

Updates in mRCC & implications for patients in Canada

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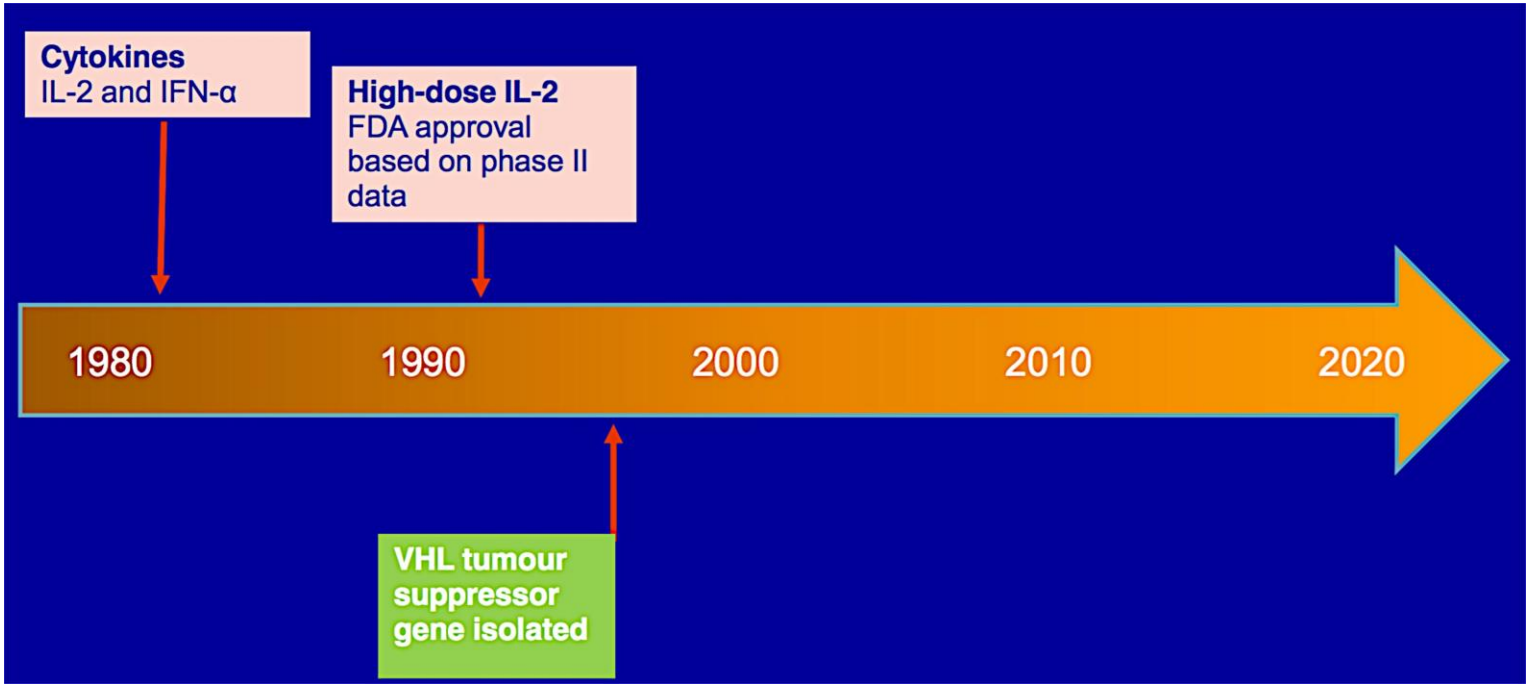
CUA WebEx, November 26th, 2018

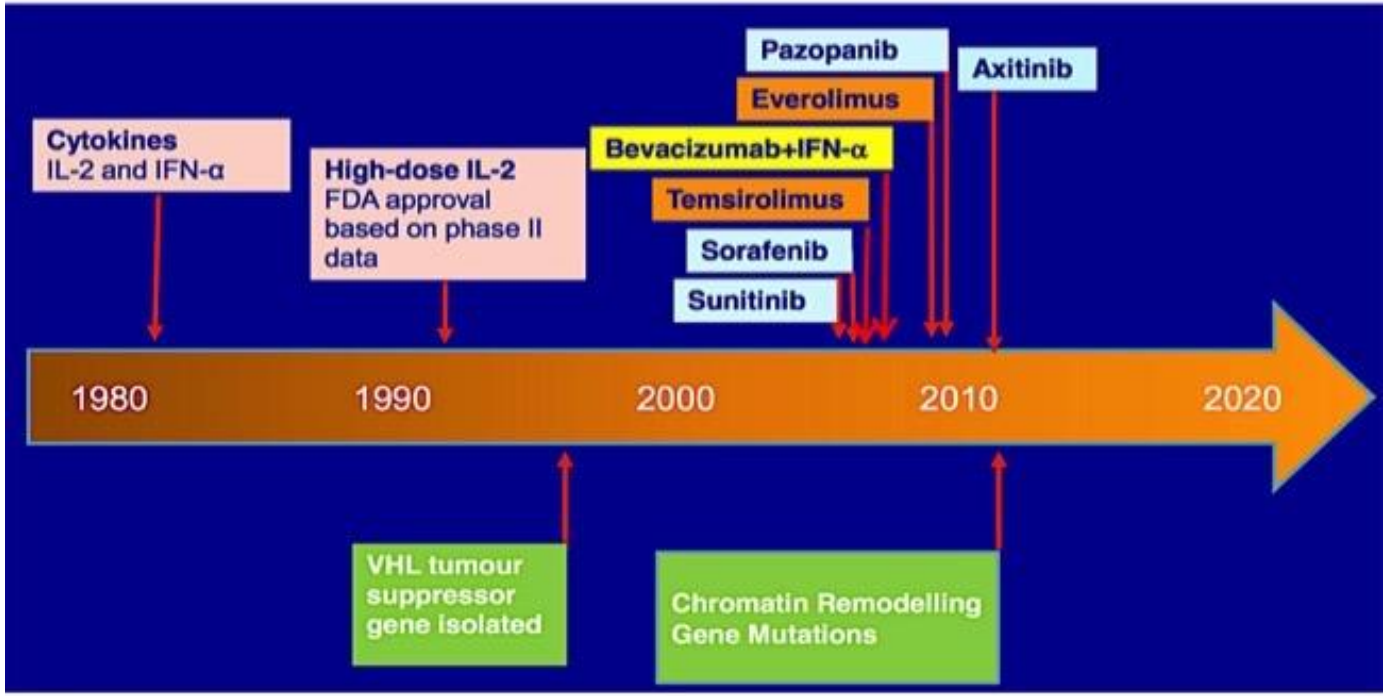
McMaster University HEALTH SCIENCES

Juravinski Cancer Centre
HAMILTON HEALTH SCIENCES

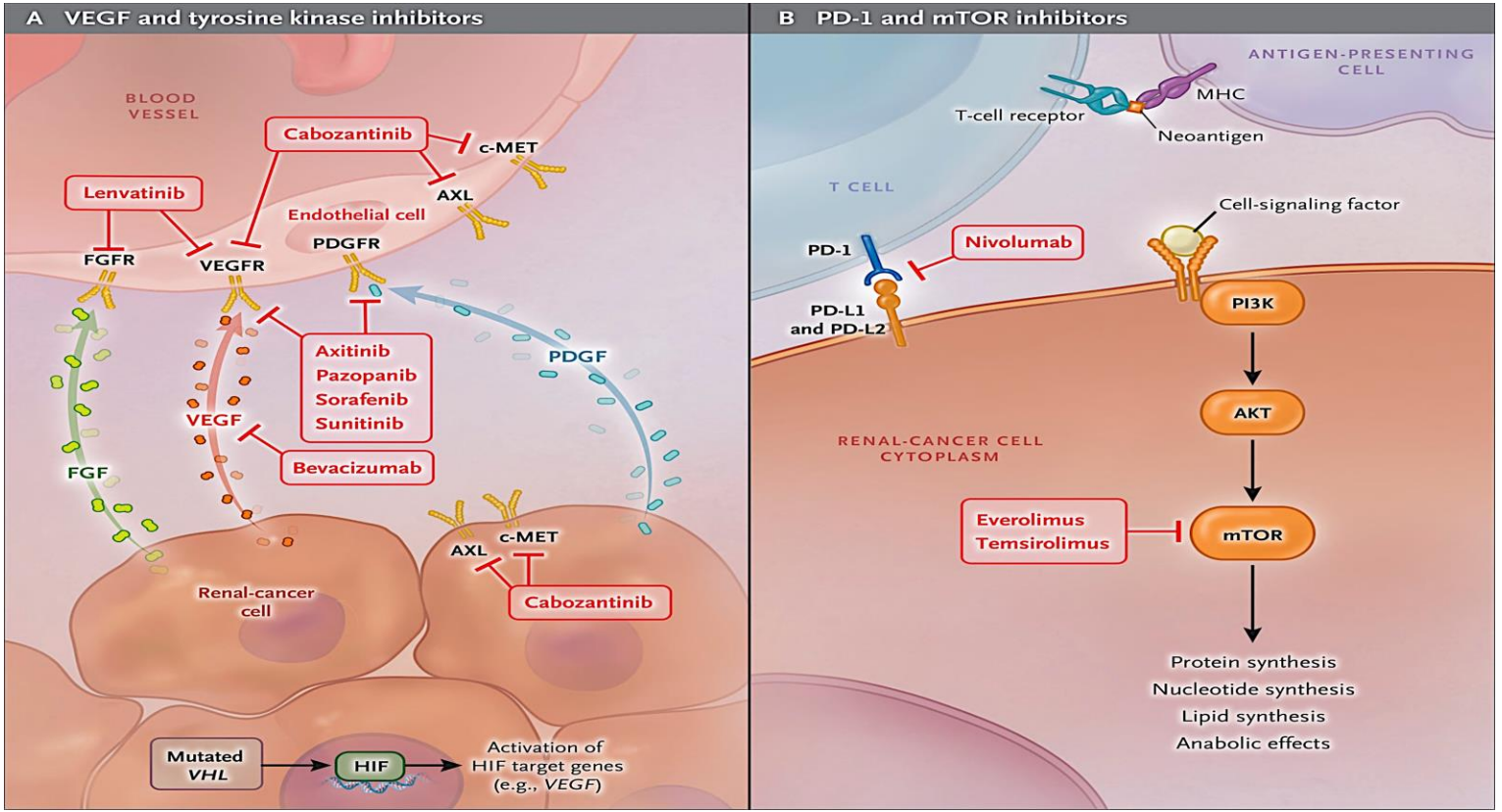
Treatments for metastatic RCC



Treatments for metastatic RCC

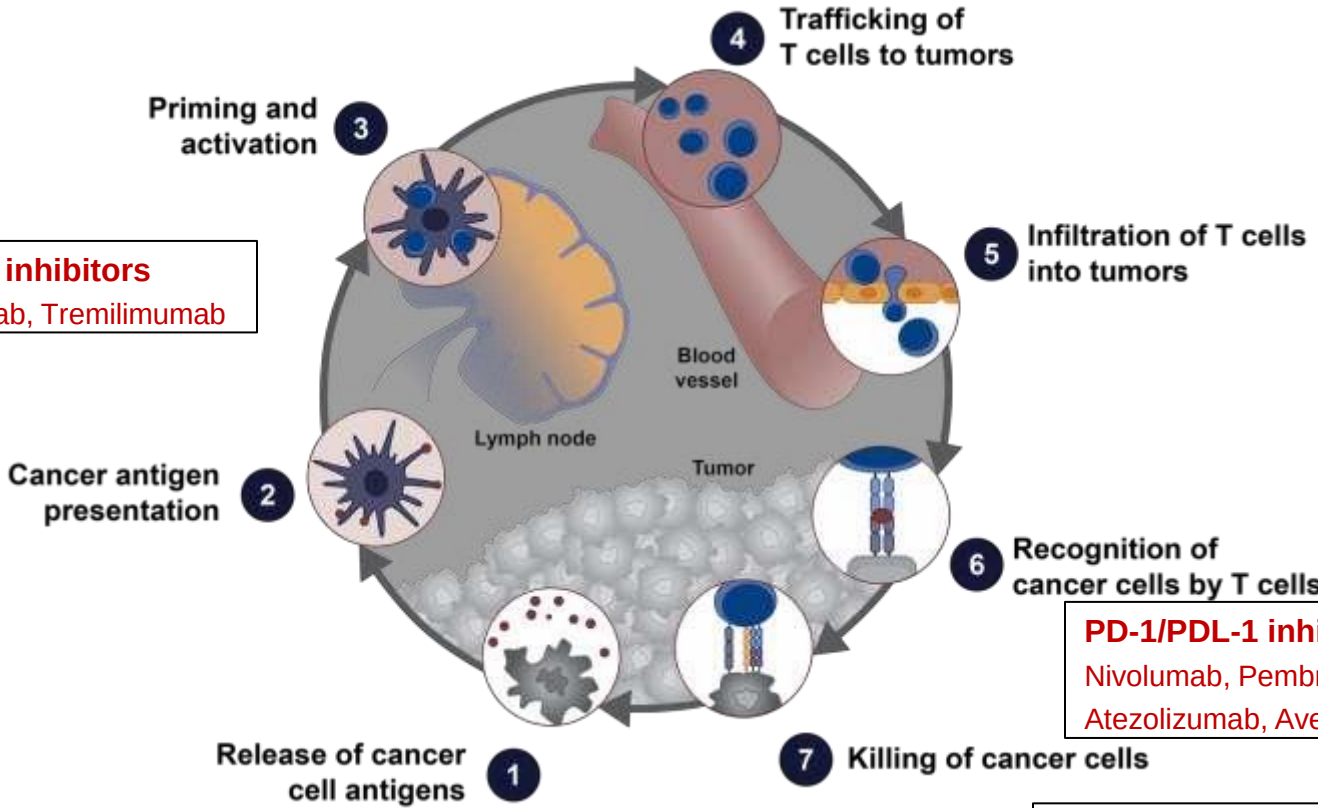


Molecular pathways and newer agents



RECENT DATA ON 1L TREATMENT OF METASTATIC RENAL CELL CARCINOMA

Synergistic strategies with immunotherapy

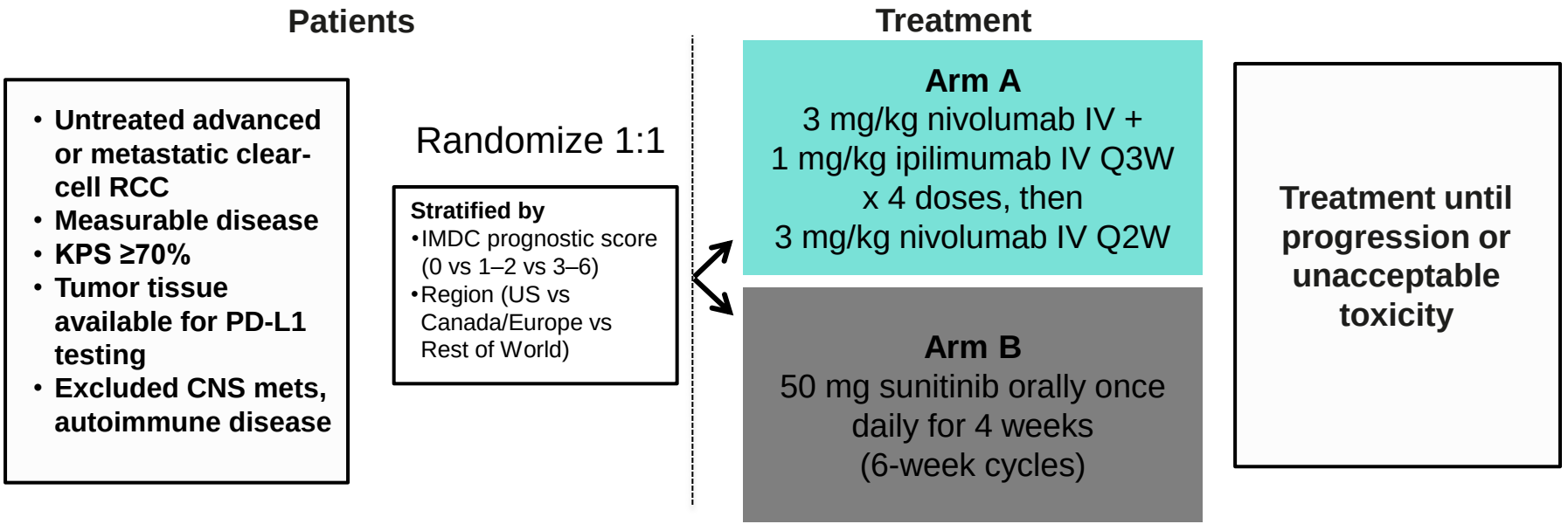


CTLA-4 inhibitors
Ipilimumab, Tremilimumab

PD-1/PDL-1 inhibitors
Nivolumab, Pembrolizumab
Atezolizumab, Avelumab, Durvalumab

1. Chen DS, Mellman I. *Immunity*. 2013;39:1-10.

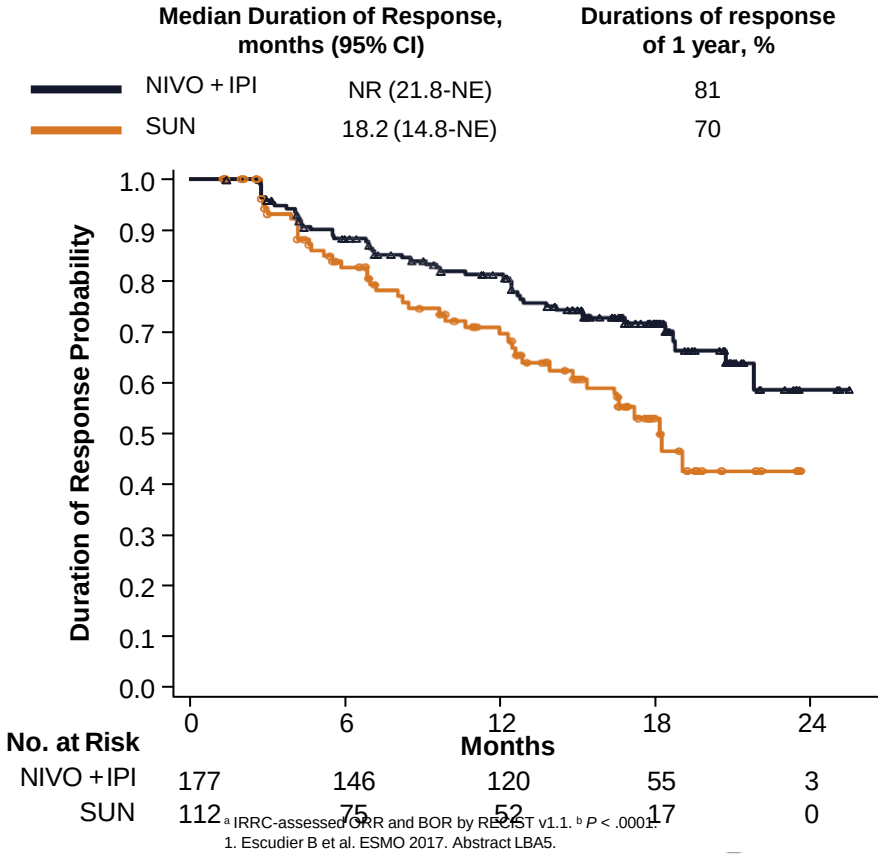
CheckMate 214: Study design



Escudier et al ESMO 2017
Motzer et al NEJM 2018

CheckMate 214: ORR per IRRC
IMDC Intermediate-/Poor-Risk Patients[1]

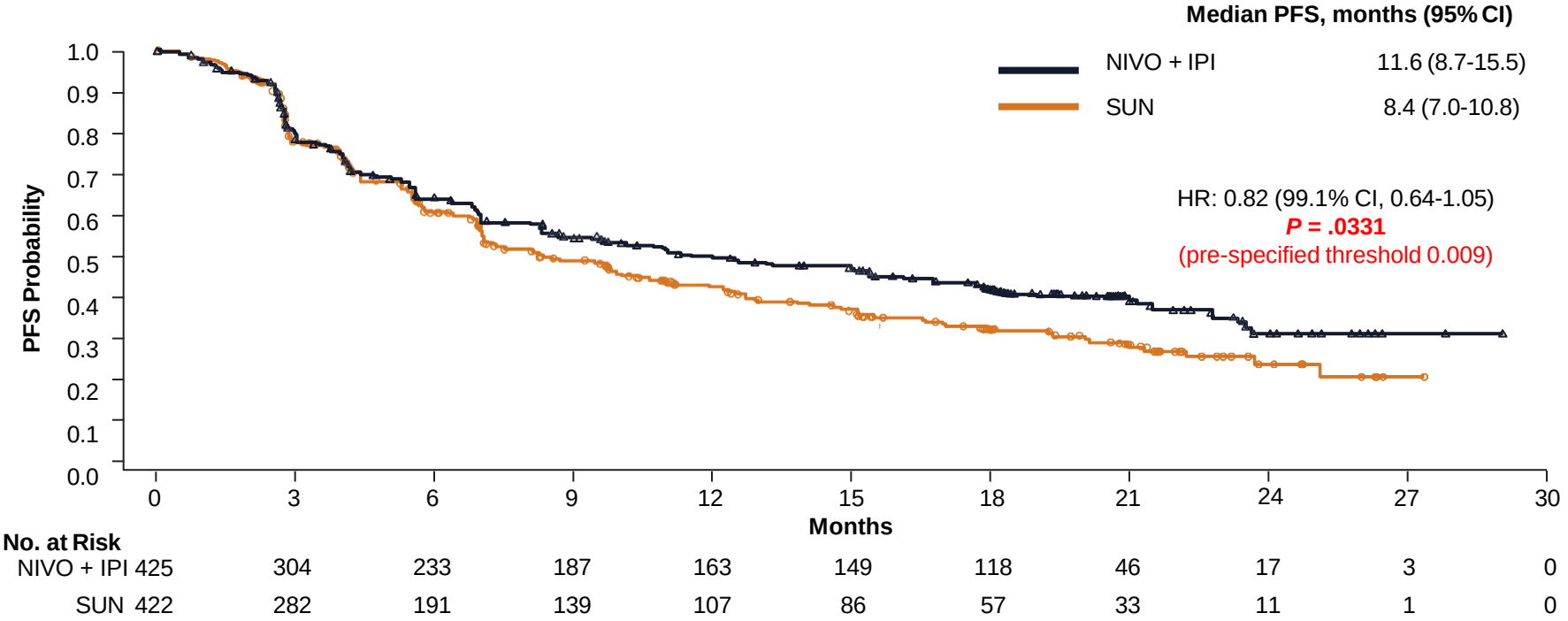
Outcome	NIVO + IPI N = 425	SUN N = 422
Confirmed ORR,[a] % (95% CI)	42 (37-47)	27 (22-31)
	P < .0001	
Confirmed BOR,[a] %		
Complete response	9[b]	1[b]
Partial response	32	25
Stable disease	31	45
Progressive disease	20	17
Unable to determine/ not reported	8	12



[a] IRRC-assessed ORR and BOR by RECIST v1.1. [b] *P* < .0001.

1. Escudier B et al. ESMO 2017. Abstract LBA5.

CheckMate 214: PFS per IRRC
IMDC Intermediate-/Poor-Risk Patients[1]



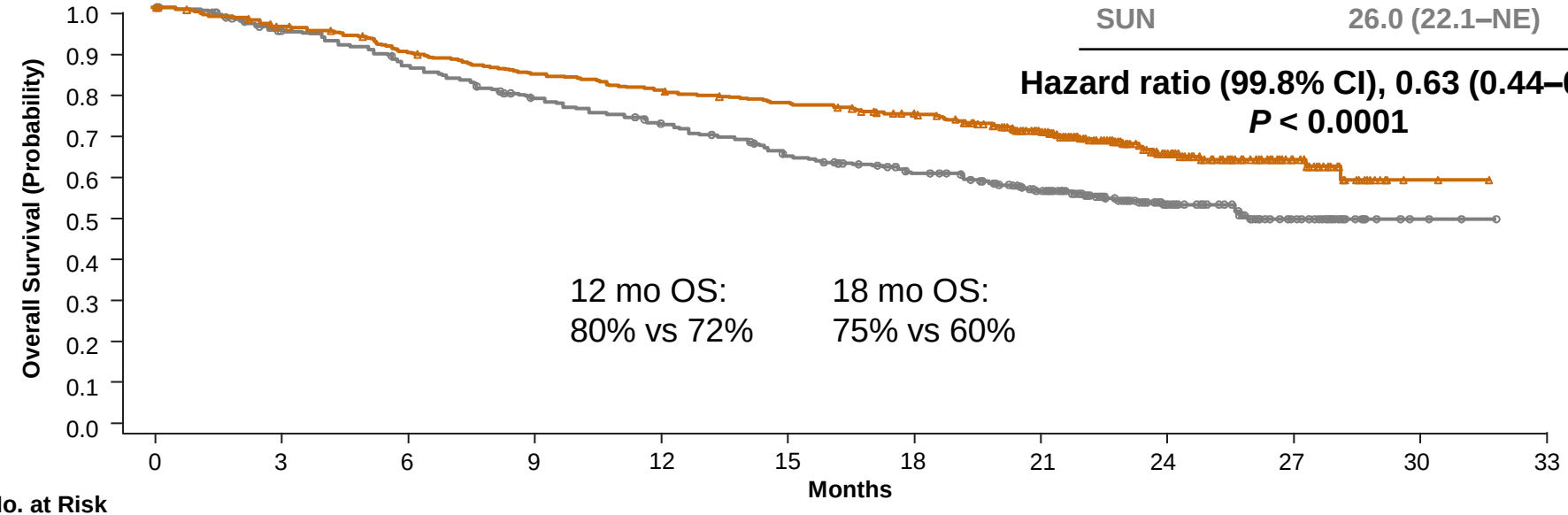
1. Escudier B et al. ESMO 2017. Abstract LBA5.

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)

Hazard ratio (99.8% CI), 0.63 (0.44–0.89)
***P* < 0.0001**



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

Escudier et al ESMO 2017

Quality of Life in Patients With Advanced Renal Cell Carcinoma in the Randomized, Open-Label CheckMate 214 Trial

David Cella,[1] Viktor Grünwald,[2] Bernard Escudier,[3] Hans J. Hammers,[4] Saby George,[5] Paul Nathan,[6] Marc-Oliver Grimm,[7] Brian I. Rini,[8] Justin Doan,[9] Cristina Ivanescu,[10] Jean Paty,[10] Sabeen Mekan,[9] Robert J. Motzer[11]

[1]Northwestern University, Chicago, IL, USA; [2]Hannover Medical School, Hannover, Germany; [3]Gustave Roussy, Villejuif, France; [4]UT Southwestern, Dallas, TX, USA; [5]Roswell Park Cancer Institute, Buffalo, NY, USA; [6]Mount Vernon Cancer Centre, Northwood, UK; [7]University Hospital of Jena, Jena, Germany; [8]Cleveland Clinic Taussig Cancer Center, Cleveland, OH, USA; [9]Bristol-Myers Squibb, Princeton, NJ, USA; [10]IQVIA, Durham, NC, USA; [11]Memorial Sloan Kettering Cancer Center, New York, NY, USA

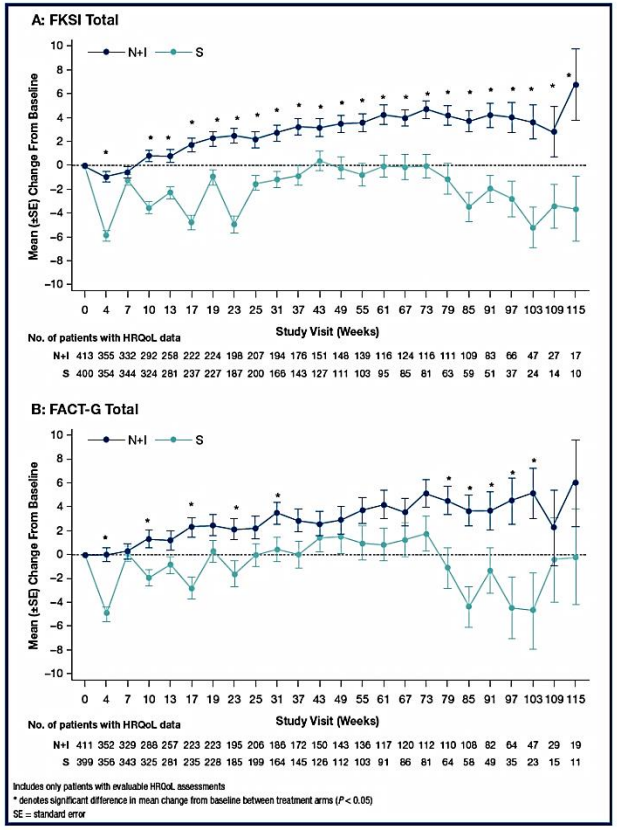
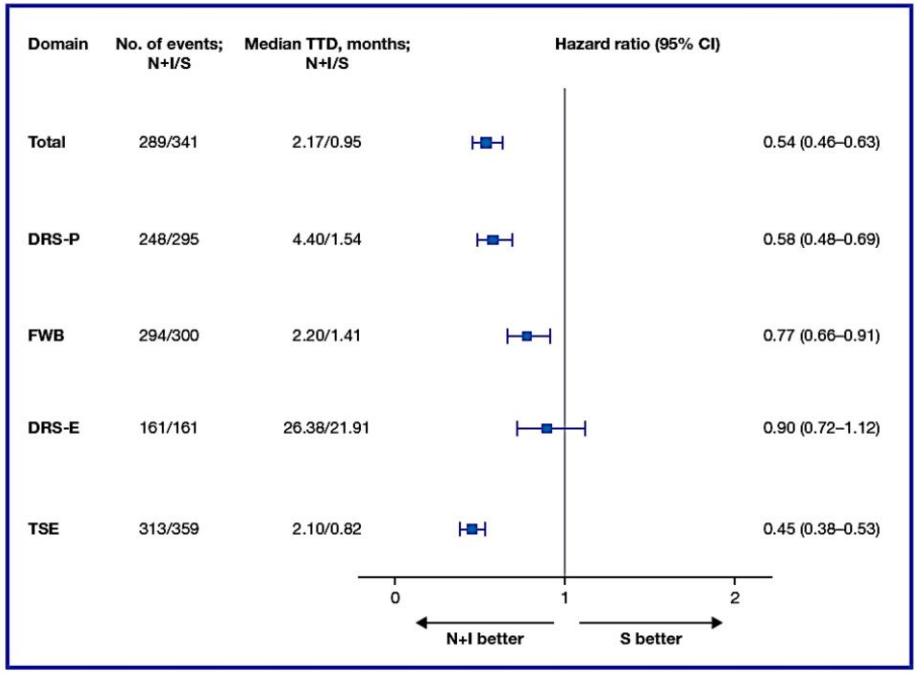


Figure 2. TTD in FKSI-19 scores



CheckMate 214: Treatment-Related Adverse Events

Event, %	NIVO + IPI N = 547		SUN N = 535	
	Any Grade	Grades 3-5	Any Grade	Grades 3-5[a]
TRAEs in ≥25% of patients	93	46	97	63
Fatigue	37	4	49	9
Pruritus	28	<1	9	0
Diarrhea	27	4	52	5
Nausea	20	2	38	1
Hypothyroidism	16	<1	25	<1
Decreased appetite	14	1	25	1
Dysgeusia	6	0	33	<1
Stomatitis	4	0	28	3
Hypertension	2	<1	40	16
Mucosal inflammation	2	0	28	3
Palmar-plantar erythrodysesthesia syndrome	1	0	43	9
TRAEs leading to discontinuation, %	**22**	**15**	**12**	**7**
Treatment-related deaths	**n = 8[b]**		**n = 4[c]**	

60% of patients treated with NIVO + IPI required systemic corticosteroids for an adverse event

[a] Two patients had grade 5 cardiac arrest. [b] Pneumonitis, immune-mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, and lung infection. [c] Cardiac arrest (n = 2), heart failure and multiple organ failure.

1. Escudier B et al. ESMO 2017. Abstract LBA5.

NEJM: "Of 436 with TRAE (select, immune-mediated), 152 required steroids (**35%**)"

ORR and PFS: IMDC favorable risk

	N = 249[a]	
~89% PD-L1 < 1% (vs 71-74% in Int/Poor risk)	**NIVO + IPI** **N = 125**	**SUN** **N = 124**
Confirmed ORR, % (95% CI) - CR rate 11% N/I vs 6% SU	**29 (21–38)**	**52 (43–61)** *P* = 0.0002
PFS, 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**	

OS **(only 37 deaths total)**: 12 month 94 vs 96%, 18 month 88% vs 93%, HR 1.45, p=0.27

Modified from: Escudier et al ESMO 2017

IMmotion 151 Phase III study

Key Eligibility:

- Treatment-naive 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

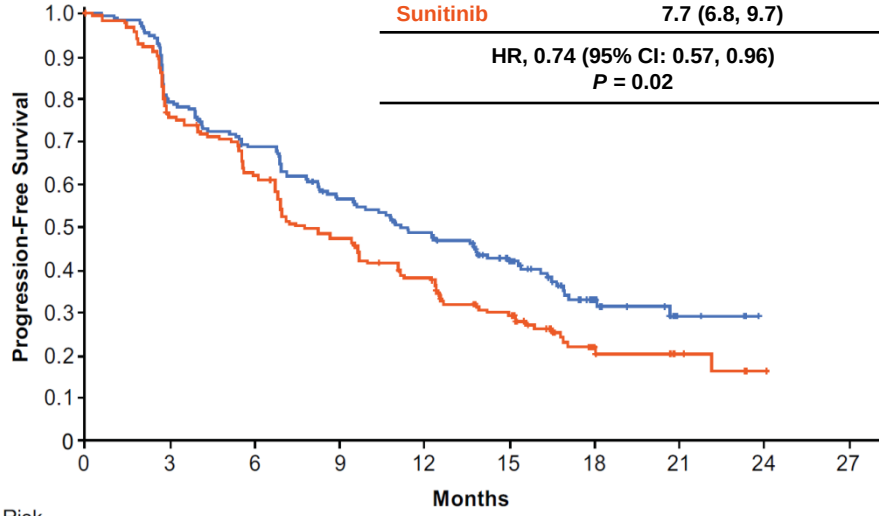
Atezolizumab 1200 mg IV q3w[b] + Bevacizumab 15 mg/kg IV q3w[b]

Sunitinib 50 mg/day orally (4 wk on, 2 wk off)

[a] ≥ 1% IC: 40% prevalence using SP142 IHC assay; [b] No dose reduction for atezolizumab or bevacizumab.

PFS IN PD-L1+

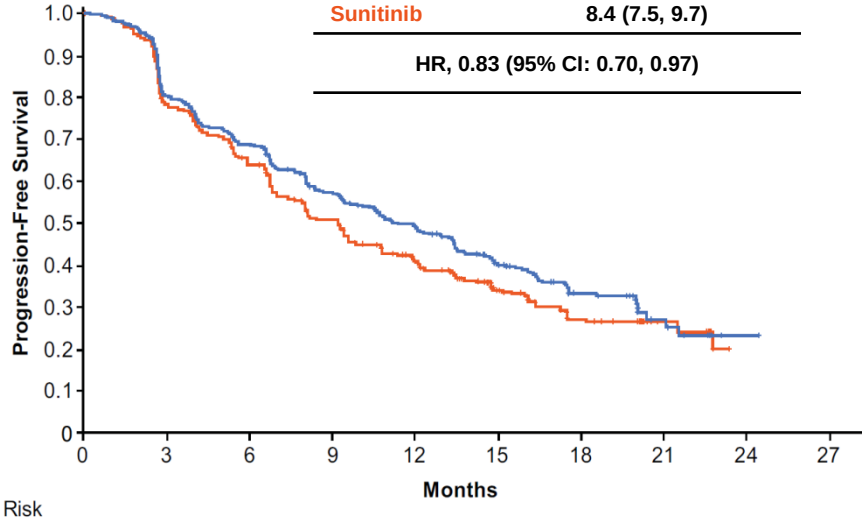
Median PFS, mo (95% CI)	
Atezo + Bev	11.2 (8.9, 15.0)
Sunitinib	7.7 (6.8, 9.7)
HR, 0.74 (95% CI: 0.57, 0.96) *P* = 0.02	



No. at Risk								
Atezo + Bev	178	137	117	94	79	55	22	5
Sunitinib	184	135	110	83	64	44	15	7	1

PFS IN ITT

Median PFS, mo (95% CI)	
Atezo + Bev	11.2 (9.6, 13.3)
Sunitinib	8.4 (7.5, 9.7)
HR, 0.83 (95% CI: 0.70, 0.97)	



No. at Risk								
Atezo + Bev	454	355	294	236	196	126	57	15	1
Sunitinib	461	346	281	211	166	105	42	14	1

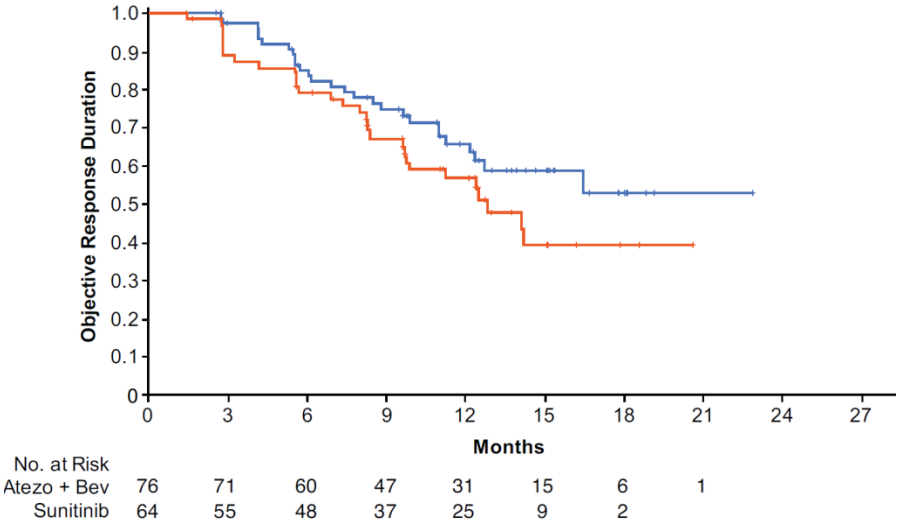
PFS assessed by investigators. Minimum follow-up, 12 mo. Median follow-up, 15 mo.

Motzer et al GU ASCO 2018

OBJECTIVE RESPONSE RATE

	PD-L1+	
	Atezo + Bev n = 178	Sunitinib n = 184
Confirmed ORR, % 95% CI	43% (35, 50)	35% (28, 42)
Complete response	9%	4%
Partial response	34%	30%
Stable disease	32%	35%
Progressive disease	19%	21%
Not evaluable[a]	7%	10%

PD-L1+	Median DOR, mo (95% CI)	Ongoing Responders, n (%)
Atezo + Bev	NR (12.4, NR)	49 (65%)
Sunitinib	12.9 (9.8, NR)	34 (53%)



NR, not reached. [a] Including patients with no post-baseline tumor assessment. ORR assessed by investigators in patients with measurable disease at baseline. Minimum follow-up, 12 mo. Median follow-up, 15 mo.

PFS AND ORR BY INDEPENDENT REVIEW COMMITTEE (IRC)

	PD-L1+		PD-L1-[a]		ITT	
	Atezo + Bev n = 178	Sunitinib n = 184	Atezo + Bev n = 276	Sunitinib n = 277[b]	Atezo + Bev n = 454	Sunitinib n = 461
Median PFS, mo (95% CI)	8.9 (6.9, 12.5)	7.2 (6.1, 11.1)	11.0 (8.3, 13.3)	8.4 (7.4, 10.1)	9.6 (8.3, 11.5)	8.3 (7.0, 9.7)
Stratified HR (95% CI)	0.93 (0.72, 1.21)		0.84 (0.67, 1.04)		0.88 (0.74, 1.04)	
Confirmed ORR, % (95% CI)	36% (29, 44)	33% (26, 40)	32% (26, 37)	30% (25, 36)	33% (29, 38)	31% (27, 36)
CR rate	15%	8%	8%	6%	11%	7%

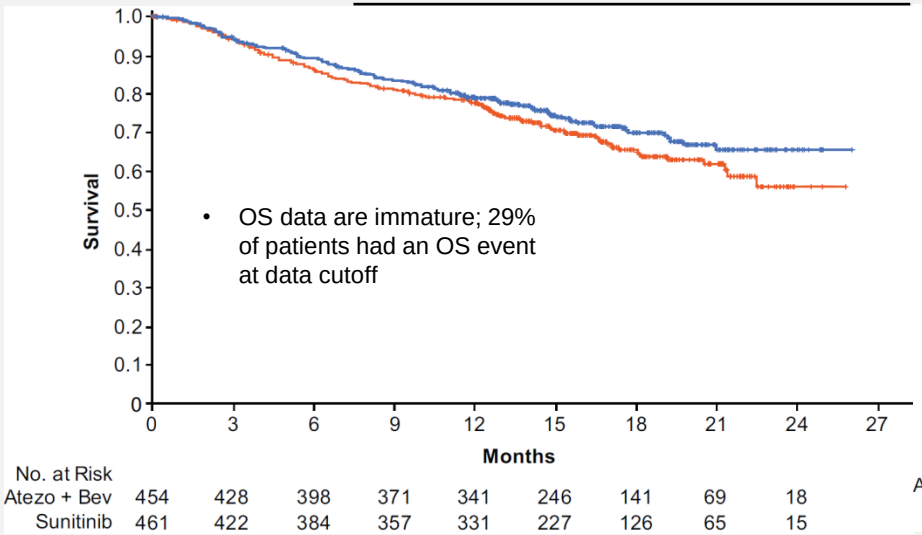
- Investigators and IRC reviewers and the sponsor were blinded to PD-L1 status
- No difference in % of therapies received after progression or % of treatment beyond progression on both arms

[a] PD-L1 negative tumors had a PD-L1 IC IHC expression < 1%. [b] n = 276 for ORR.

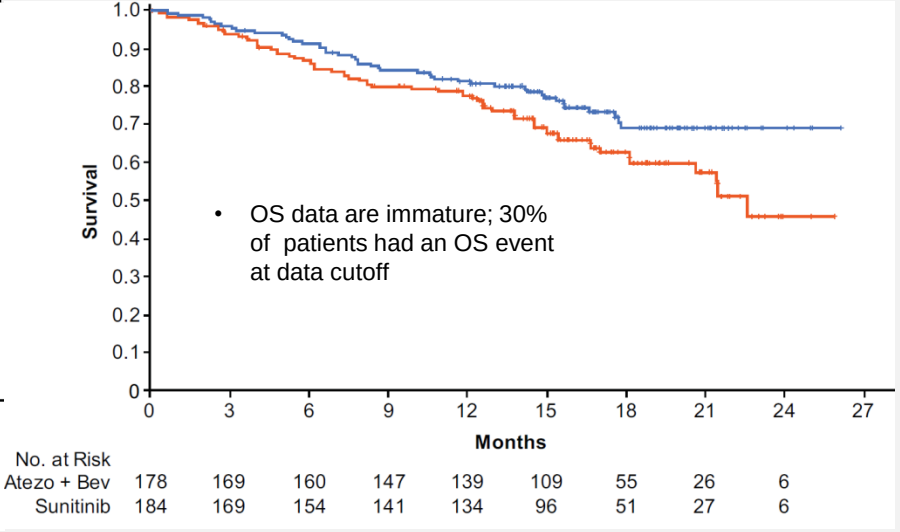
Co-Primary Endpoint

OVERALL SURVIVAL IN ITT & PD-L1+ (IMMATURE)

ITT Median OS, mo (95% CI)	
Atezo + Bev	Not reached
Sunitinib	Not reached
HR, 0.81 (95% CI: 0.63, 1.03) *P* = 0.09	



PD-L1+ Median OS, mo (95% CI)	
Atezo + Bev	Not reached
Sunitinib	23.3 (21.3, NR)
HR, 0.68 (95% CI: 0.46, 1.00)	



Minimum follow-up, 12 mo. Median of follow-up, 15 mo. Event/patient ratio: 27% for atezo + bev, 31% for sunitinib.
The OS analysis did not pass the *P* value boundary of alpha = 0.0009 at the first interim analysis.

MUNICH 2018 ESMO congress

JAVELIN Renal 101: Randomized Phase 3 Trial of Avelumab + Axitinib vs Sunitinib as First-Line Treatment of Advanced Renal Cell Carcinoma

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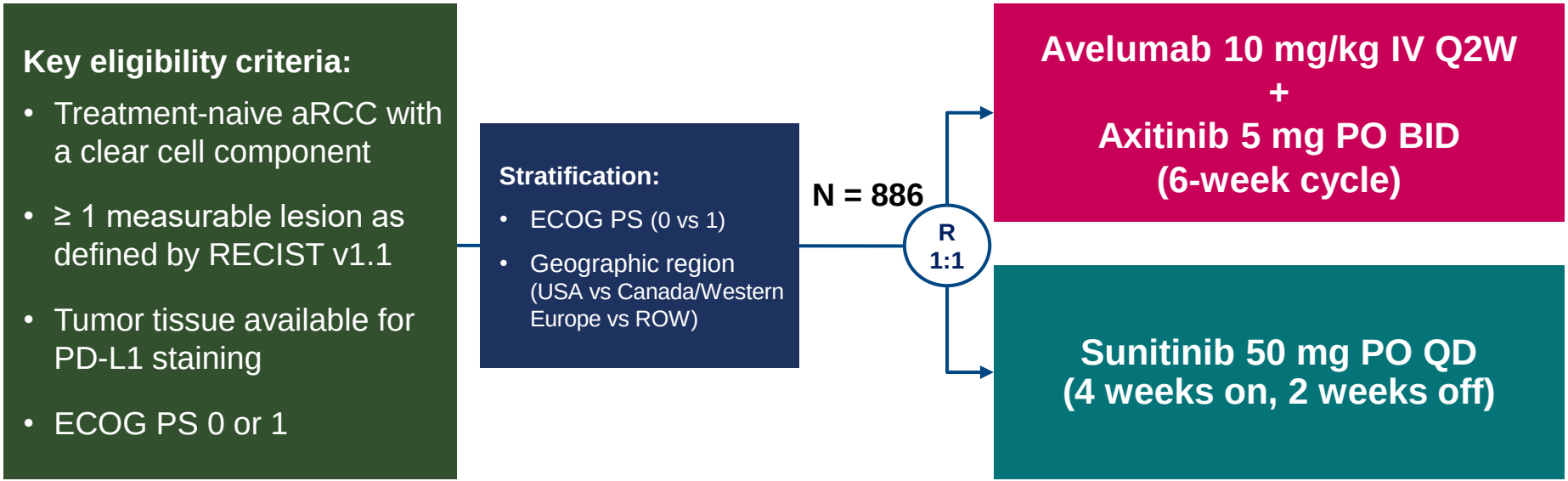
[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Private Medical Institution Euromedservice, Pushkin, St. Petersburg, Russian Federation; [3]Netherlands Cancer Institute, Amsterdam, Netherlands; [4]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [5]Institut Gustave Roussy, Villejuif, France; [6]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]British Columbia Cancer Agency, Vancouver, BC, Canada; [8]Centre Léon Bérard, Lyon, France; [9]Osaka University Hospital, Osaka, Japan; [10]University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; [11]Macquarie University, Sydney, NSW, Australia; [12]Chaim Sheba Medical Center and Tel Aviv University Sackler School of Medicine, Tel HaShomer, Israel; [13]Medical University of Vienna; Department of Medicine I, Clinical Division of Oncology and Comprehensive Cancer Center, Vienna, Austria; [14]The Royal Marsden NHS Foundation Trust, London, UK; [15]Georgetown Lombardi Comprehensive Cancer Center Washington, D.C., USA; [16]Pfizer Inc, Cambridge, MA, USA; [17]Pfizer Inc, San Diego, CA, USA; [18]Pfizer SRL, Lombardia, Italy; [19]The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Abstract No. LBA6_PR

JAVELIN Renal 101: study design

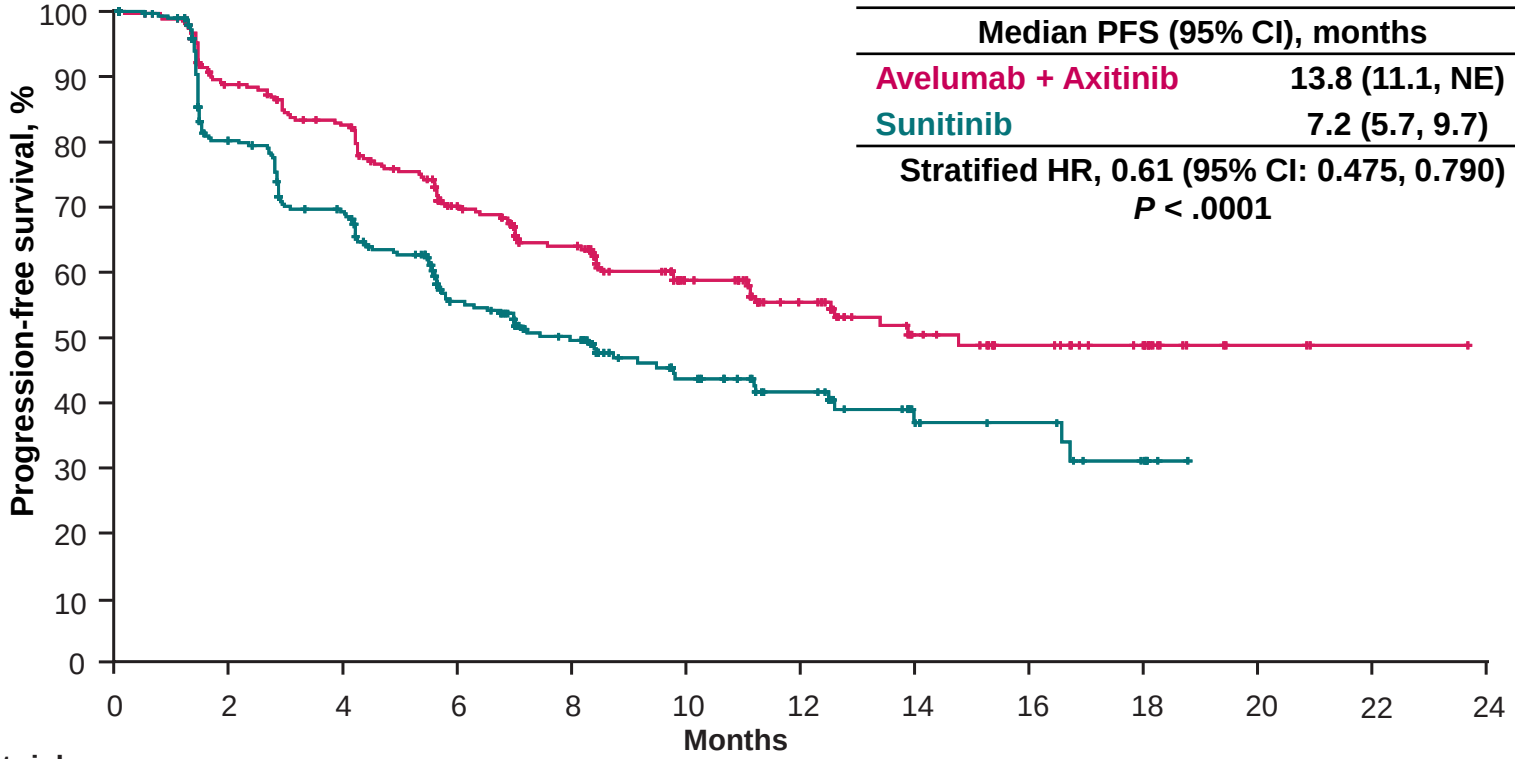


- **Primary endpoints**
  - PFS by RECIST v1.1 per independent review committee (IRC) in patients with PD-L1+ tumors (PD-L1+ group)*
  - OS in the PD-L1+ group

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

PFS per IRC in the PD-L1+ group

Primary endpoint



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

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

Number at risk

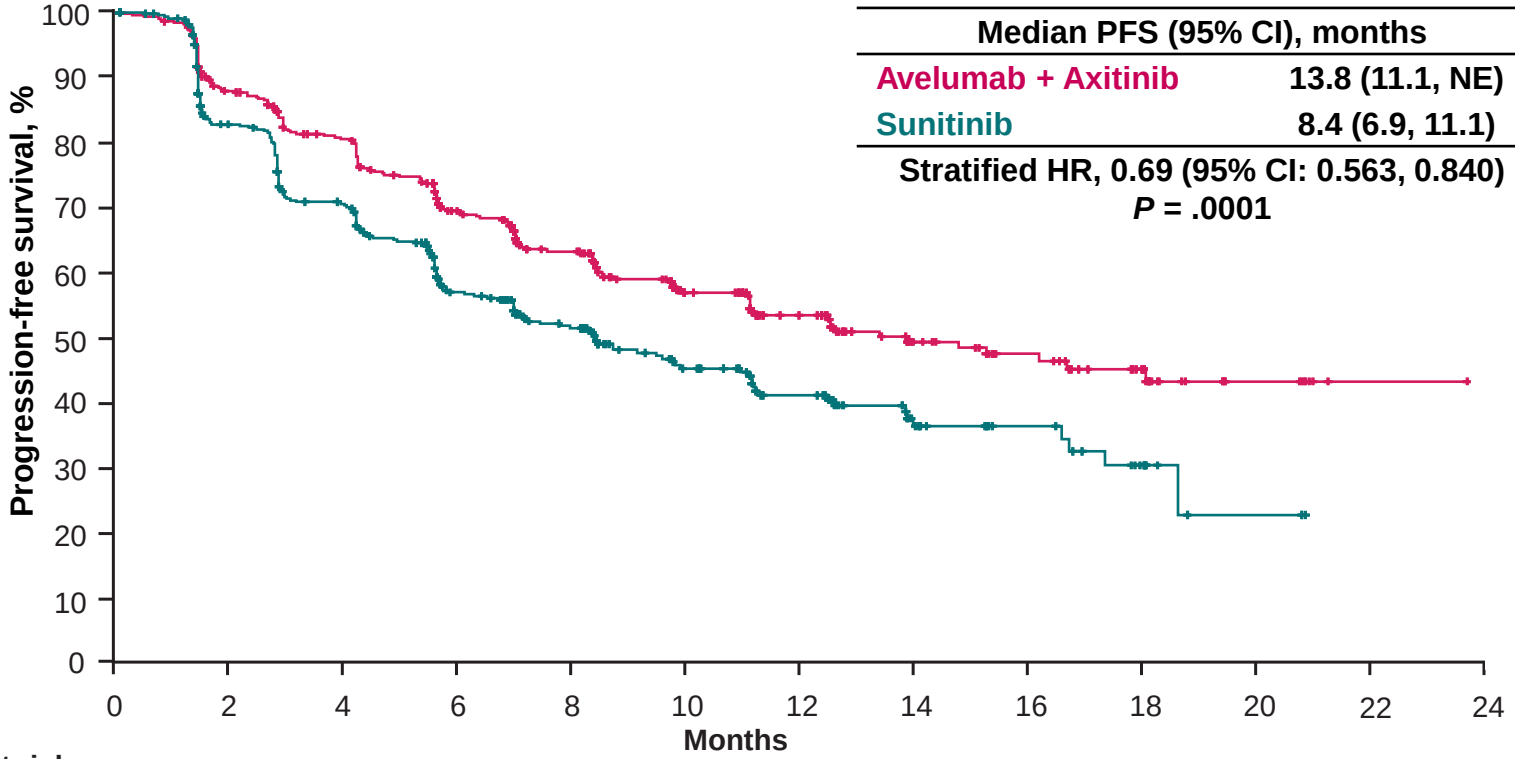
Avel + Axit:	270	227	205	154	120	76	53	32	23	13	3	1	0
Sunitinib:	290	210	174	119	85	49	35	16	13	5	0		

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

NE, not estimable.

PFS per IRC in the overall population

Key secondary endpoint



Median PFS (95% CI), months	
Avelumab + Axitinib	13.8 (11.1, NE)
Sunitinib	8.4 (6.9, 11.1)

Stratified HR, 0.69 (95% CI: 0.563, 0.840)
P = .0001

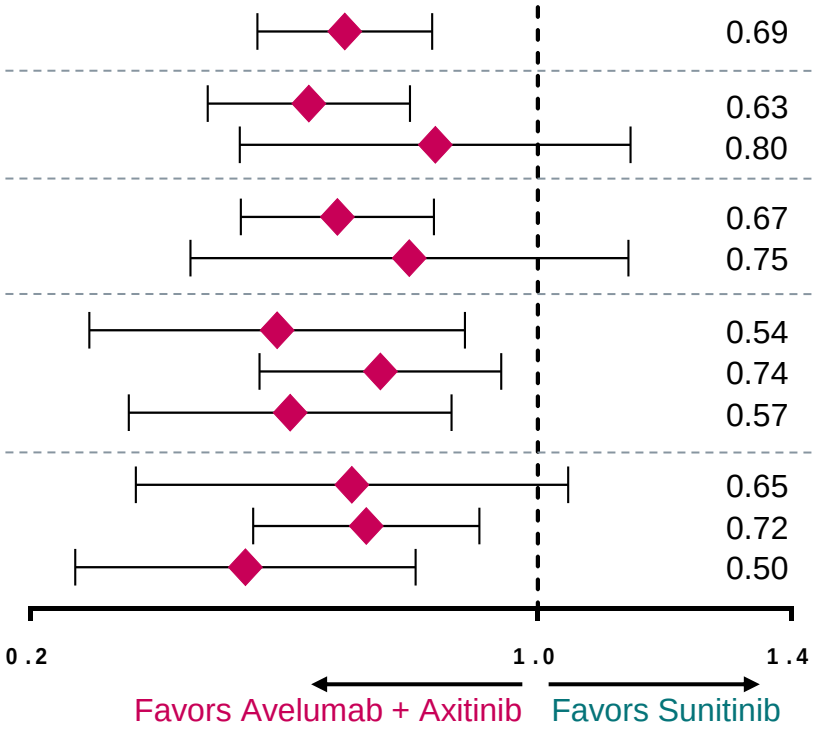
Number at risk

Avel + Axit:	442	364	321	250	193	127	94	57	42	24	8	1	0
Sunitinib:	444	329	271	192	144	90	64	29	20	8	2	0	

Minimum follow-up, 6 months. Median follow-up, 10.8 months (avelumab + axitinib) and 8.6 months (sunitinib).
The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* = .001).

PFS per IRC in key subgroups

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



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

Confirmed objective response

Secondary endpoint

Per IRC	PD-L1+ group (N = 560)		Overall population (N = 886)	
	Avelumab + Axitinib (N = 270)	Sunitinib (N = 290)	Avelumab + Axitinib (N = 442)	Sunitinib (N = 444)
Objective response rate (95% CI), %	**55 (49.0, 61.2)**	**26 (20.6, 30.9)**	**51 (46.6, 56.1)**	**26 (21.7, 30.0)**
Best overall response, %*				
Complete response	4	2	3	2
Partial response	51	23	48	24
Stable disease	27	43	30	46
Progressive disease	11	22	12	19
Not evaluable†	4	7	6	8
Patients with ongoing response, %‡	73	65	70	71
Per investigator assessment				
Objective response rate (95% CI), %	**62 (55.8, 67.7)**	**30 (24.5, 35.3)**	**56 (51.1, 60.6)**	**30 (25.9, 34.7)**
Best overall response, %				
Complete response	4	3	3	2
Partial response	58	27	53	28

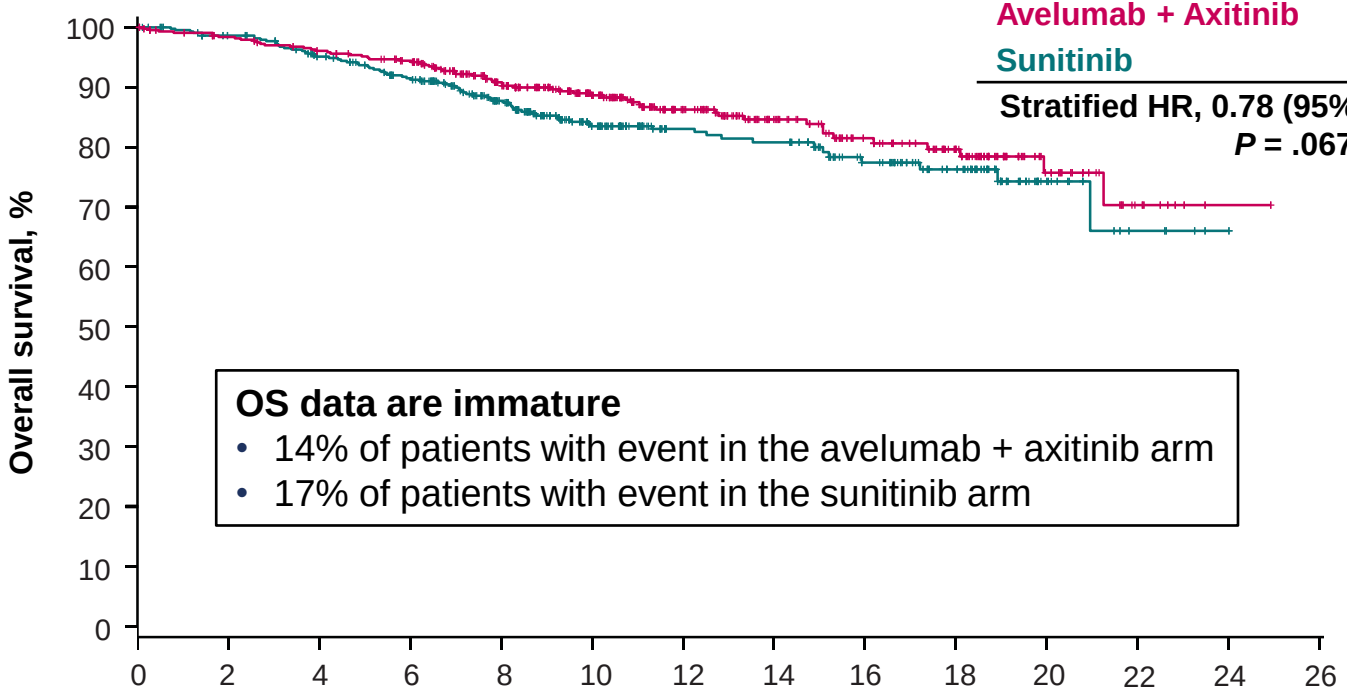
Median duration of response was not yet reached in either treatment arm in either population.

* Patients without target lesions at baseline per IRC who achieved non-complete response/non-progressive disease: 3% (avelumab + axitinib) and 2% (sunitinib) in the PD-L1+ group; 2% (avelumab + axitinib) and 2% (sunitinib) in the overall population. † Including patients with no postbaseline assessments. ‡ In patients with confirmed complete or partial response.

OS in the overall population

Median OS (95% CI), months	
Avelumab + Axitinib	Not reached
Sunitinib	Not reached

Stratified HR, 0.78 (95% CI: 0.554, 1.084)
***P* = .0679**



Number at risk

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

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

JAVELIN Renal 101: efficacy summary

	PD-L1+ group (N = 560)		Overall population (N = 886)	
	Avelumab + Axitinib (N = 270)	Sunitinib (N = 290)	Avelumab + Axitinib (N = 442)	Sunitinib (N = 444)
PFS per IRC*				
Median, months	13.8	7.2	13.8	8.4
95% CI	11.1, NE	5.7, 9.7	11.1, NE	6.9, 11.1
Benefit vs sunitinib (HR; *P* value)	0.61; *P* < .0001	-	0.69; *P* = .0001	-
Objective response rate per IRC, %	55	26	51	26
95% CI	49.0, 61.2	20.6, 30.9	46.6, 56.1	21.7, 30.0
PFS per investigator assessment				
Median, months	13.3	8.2	12.5	8.4
95% CI	9.8, NE	6.9, 8.5	11.1, 15.2	8.2, 9.7
Benefit vs sunitinib (HR; *P* value)	0.51; *P* < .0001	-	0.64; *P* < .0001	-
Objective response rate per investigator assessment, %	62	30	56	30
95% CI	55.8, 67.7	24.5, 35.3	51.1, 60.6	25.9, 34.7

* PFS benefit per IRC was observed in patients regardless of PD-L1 status and in all prognostic risk groups.

Conclusions

- JAVELIN Renal 101 demonstrated longer PFS and higher ORR for avelumab + axitinib compared with sunitinib for treatment-naïve mRCC patients
- Benefit was observed in patients regardless of PD-L1 status and in all prognostic risk groups
- Combination demonstrated a favorable safety profile
- **Continued follow-up for overall survival**

WHERE DO WE GO FROM HERE?

Combination strategies with IO backbone

	I-O + TKI		I-O + I-O	I-O + VEGF TKI	I-O + VEGF mAb	PD-1/PD-L1 monothreapy		TKI monotherapy
TRIAL	**Pembrolizumab + Axitinib[1]**	**Pembrolizumab + Lenvatinib[2]**	**Nivolumab + Ipilimumab[4,5]**	**Avelumab + Axitinib[3]**	**Atezolizumab + Bevacizumab[6]**	***Pembrolizumab[7]***	***Atezolizumab[8]***	***Sunitinib[6]***
Phase	IB	IB/II	III	III	III	II	II	III
N	52	30	425 *(Int/Poor risk)*	442 (overall)	454	110	103	461
Prior therapy?	No	Yes	No	No	No	No	No	No
ORR	**73%**	**63%**	**42%**	**51%**	**37%**	**38%**	**25%**	**33%**

[1]NCT02133742, Atkins et al. Lancet Oncol 2018; [2]NCT02501096, Lee et al. ESMO 2017; [3]NCT02493751, Motzer et al. ESMO 2018; [4,5]NCT02231749 Escudier et al. ESMO 2017, Motzer et al. SITC 2017; [6]NCT01984242 Motzer et al. ASCO GU 2018; [7] NCT02853344 McDermott et al, ASCO 2018; [8]NCT01984242 Atkins et al, ASCO 2017.

Courtesy: AK Lalani, Z. Bakouny, T Choueiri

KEYNOTE-426 PRESS RELEASE

Merck's KEYTRUDA® (pembrolizumab) in Combination with Pfizer's Inlyta® (axitinib) Significantly Improved Overall Survival (OS) and Progression-free Survival (PFS) as First-Line Therapy for Advanced or Metastatic Renal Cell Carcinoma

KEYTRUDA is First Anti-PD-1 Therapy in Combination to Improve Both OS and PFS in Advanced or Metastatic RCC, the Most Common Type of Kidney Cancer

Pivotal Phase 3 KEYNOTE-426 Trial Met Both Primary Endpoints; Data to be Filed with Global Regulatory Authorities

October 18, 2018 06:57 AM Eastern Daylight Time

KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE: MRK), known as MSD outside the United States and Canada, announced today that the pivotal Phase 3 KEYNOTE-426 trial investigating KEYTRUDA® (pembrolizumab), Merck's anti-PD-1 therapy, in combination with Inlyta® (axitinib), Pfizer's tyrosine kinase inhibitor, met both primary endpoints of overall survival (OS) and progression-free survival (PFS) in the first-line treatment of advanced or metastatic renal cell carcinoma (RCC), the most common type of kidney cancer. Based on the first interim analysis by the independent Data Monitoring Committee (DMC), the KEYTRUDA plus Inlyta combination resulted in statistically significant and clinically meaningful improvements in OS and PFS, compared to sunitinib monotherapy. The study also met the key secondary endpoint of objective response rate (ORR), with significant improvements for the KEYTRUDA and Inlyta combination compared with sunitinib monotherapy. Results for OS, PFS and ORR were consistent regardless of PD-L1 expression and across all risk groups. The safety profile of

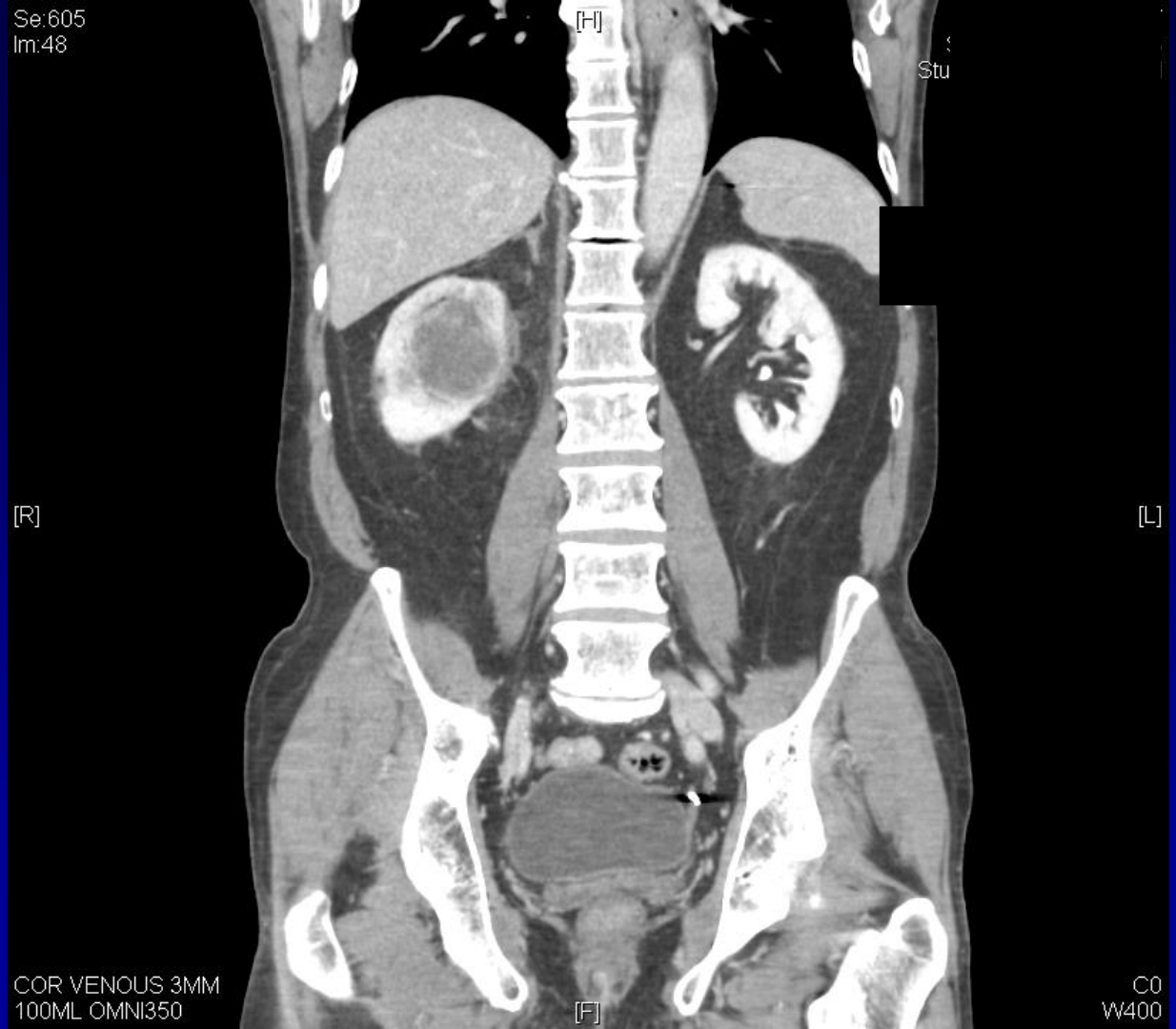
Metastatic Renal Cell Carcinoma

Case Study on Sequencing Favorable Risk Disease

Anil Kapoor, MD, FRCSC
Professor of Surgery (Urology), McMaster University
Hamilton, Ontario

Clinical Case

- 69 year old male
- Presented with hematuria
- Ex-smoker
- CBC normal; Calcium normal
- CT Scan - 6 cm right renal mass, no metastases (tiny pulmonary nodules)


Se:605
Im:48
[H]
Stu
[R]
[L]
COR VENOUS 3MM
100ML OMNI350
[F]
C0
W400

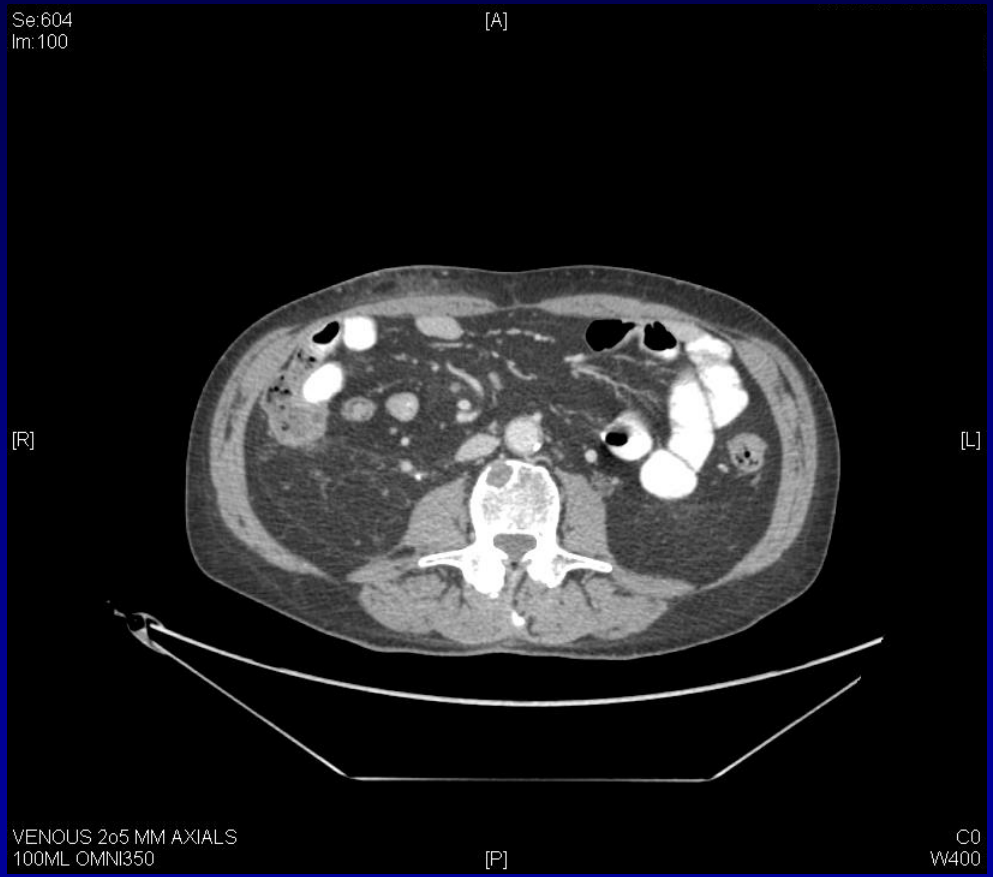
- Biopsy necessary ?
- Underwent Laparoscopic Right Radical Nephrectomy; no surgical issues
- Pathology – ccRCC, T3A, N0, M0; grade ¾
- Considered “High Risk for Recurrence”

- Adjuvant Therapy ?
  - IO Clinical Trial
  - TKI – sunitinib

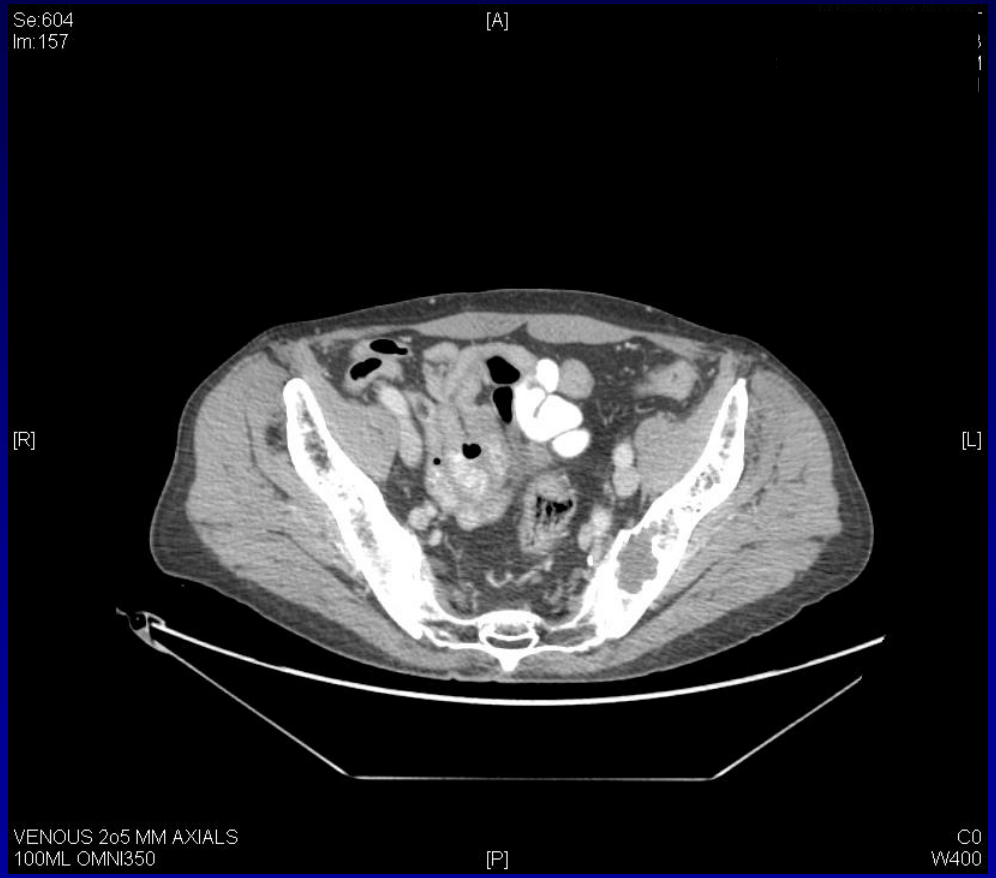
Patient chose surveillance, deferred clinical trial

- Imaging follow – up as per CUA guidelines:
  - Negative until 2 years
  - Back pain – prompts CT
  - Spine metastases; Iliac bone metastases and multiple lung metastases
  - Bloodwork – normal CBC, Calcium, LDH
  - Good performance status
  - IMDC criteria – 0 – Favorable Risk

Met RCC –mets to spine



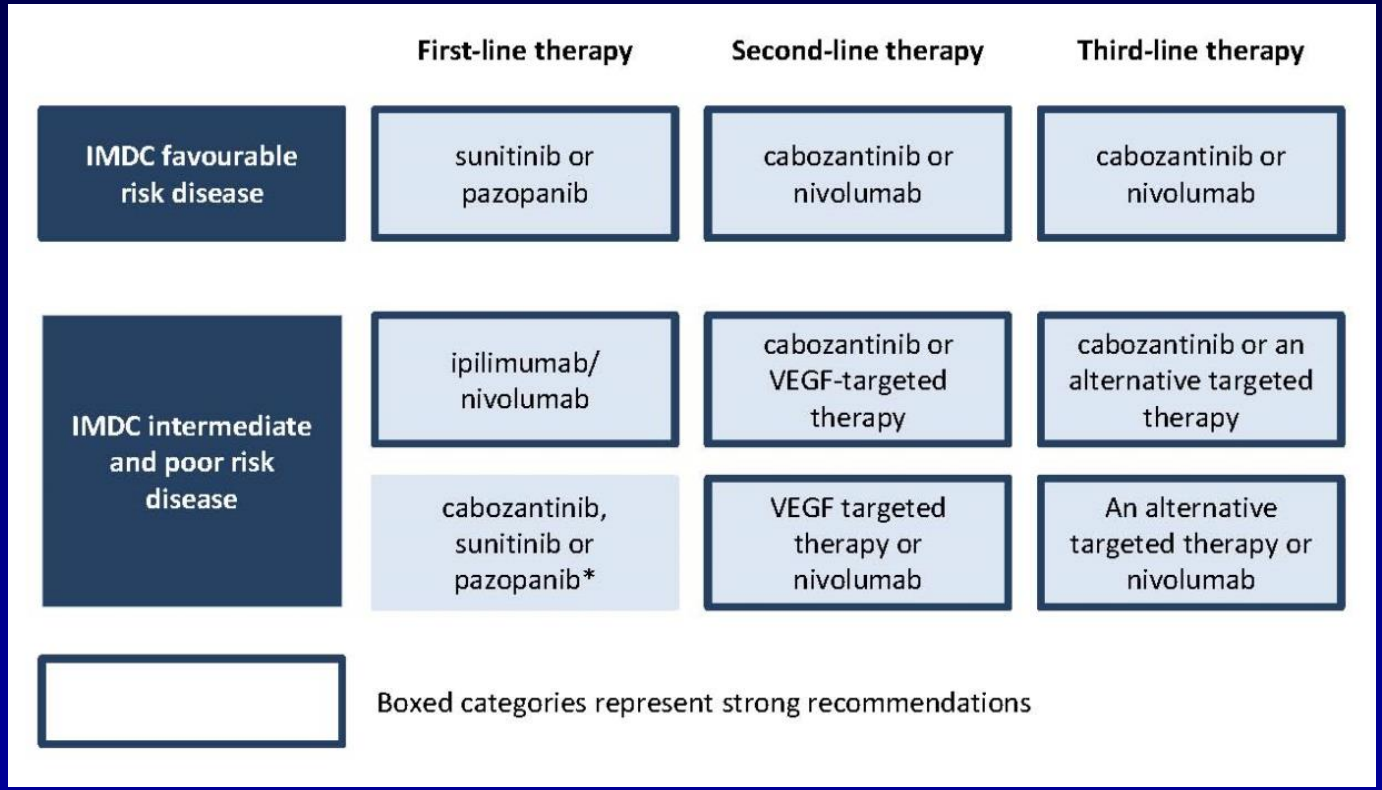
Met RCC –mets to iliac



First-line Options in Canada 2018

- Clinical trial
- Immunotherapy
  - Ipilimumab/Nivolumab
- VEGF targeted therapy
  - Sunitinib
  - Pazopanib

EAU 2018 Guidelines



IMDC=The International Metastatic Renal Cell Carcinoma Database Consortium; VEGF=vascular endothelial growth factor.

***pazopanib for intermediate risk only.**

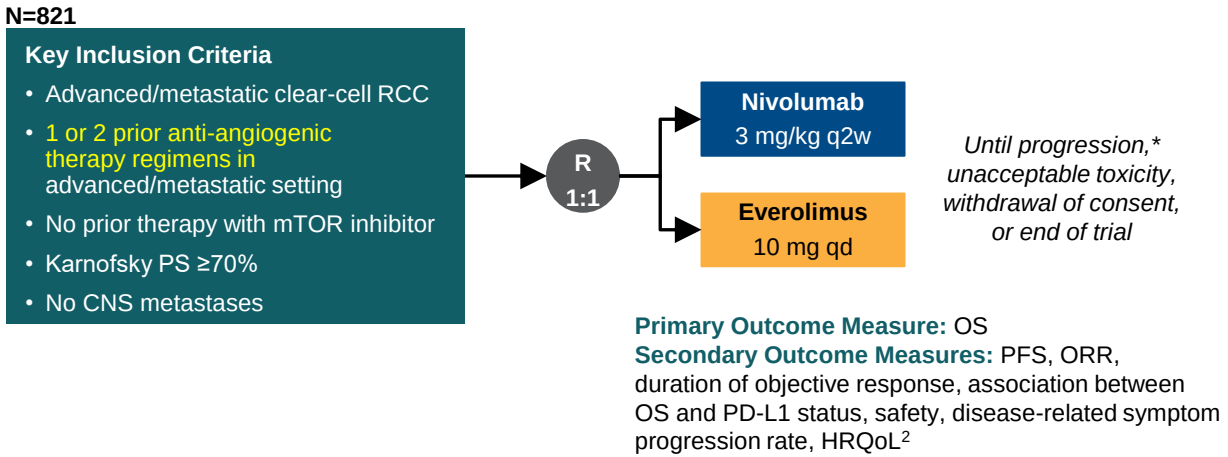
First-line Treatment

- Started on Pazopanib 800 mg daily
- Minimal toxicity
- SBRT to spine
- Stable disease for 12 months
- Progression of lung nodules

Second-line Options

- Nivolumab
- Cabozantinib
- Axitinib
- (Lenvatinib/Everolimus)
- Clinical Trial
- (Everolimus)

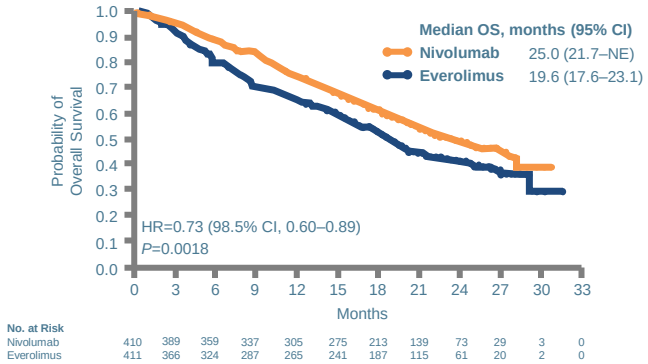
CHECKMATE 025: PHASE 3 TRIAL OF NIVOLUMAB VERSUS EVEROLIMUS IN PRETREATED METASTATIC RCC



*Treatment beyond progression (RECIST 1.1) was allowed if investigator-assessed clinical benefit was achieved and treatment was well tolerated.

1. Motzer RJ et al. *N Engl J Med*. 2015. 2. Cella DF et al. Poster presentation at ASCO 2016. 4549.

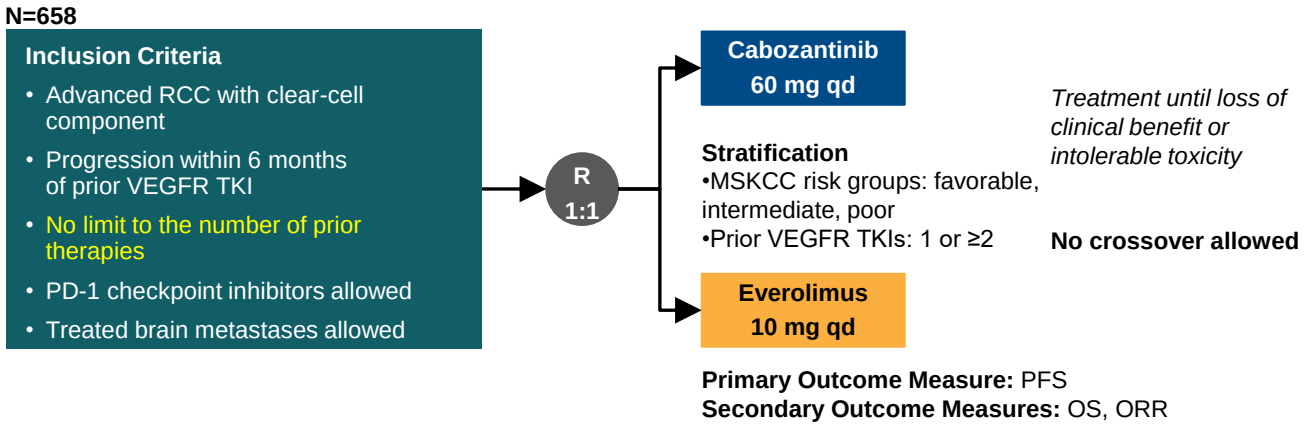
Nivolumab Phase 3 Study (CheckMate 025): OS and ORR



Investigator ORR: 25% vs 5%; odds ratio 5.98; 95% CI, 3.68–9.72; P<0.001

Motzer RJ, et al. N Engl J Med 2015;373:1803–13.

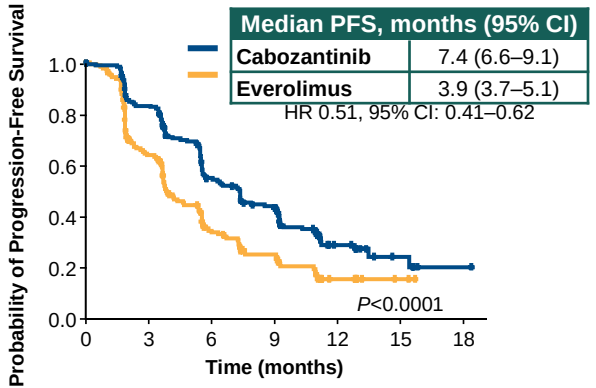
METEOR: PHASE 3 TRIAL OF CABOZANTINIB VERSUS EVEROLIMUS IN ADVANCED RCC



Choueiri TK et al. Oral presentation at ASCO 2016. 4506.

METEOR: ORR, PFS, AND OS BENEFIT

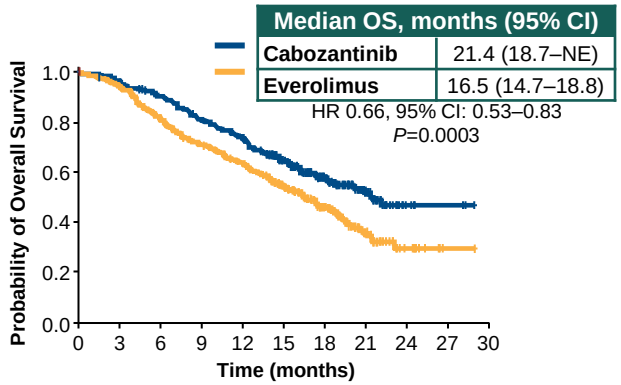
	Cabozantinib n=330		Everolimus n=328	
	IRC	Investigator	IRC	Investigator
ORR (95% CI)*	17 (13–22)†	24 (19–29)†	3 (2–6)	4 (2–7)



Number of patients at risk

Cabozantinib	330	261	148	88	20	6	2
Everolimus	328	174	72	37	10	2	0

Adapted from Choueiri et al. 2016.



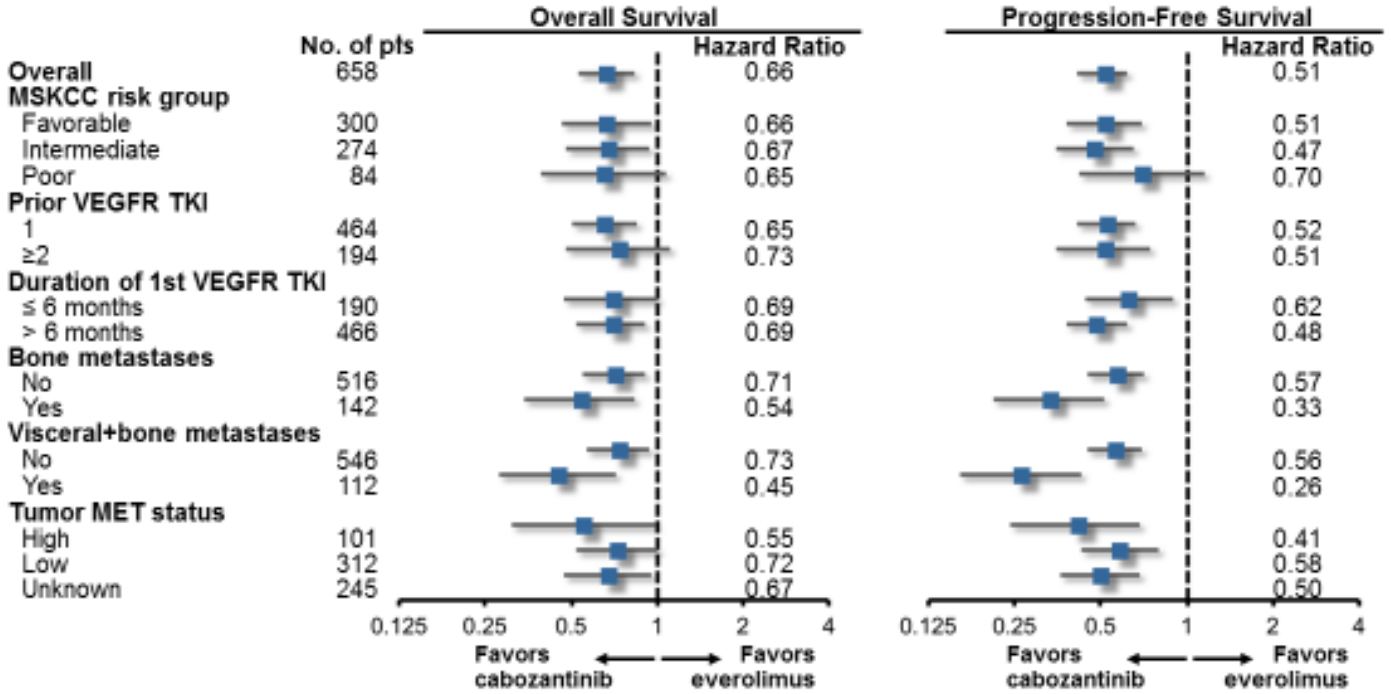
Number of patients at risk

Cabozantinib	330	318	296	264	239	178	105	41	6	3	0
Everolimus	328	307	262	229	202	141	82	32	8	1	0

Adapted from Choueiri et al. 2016.

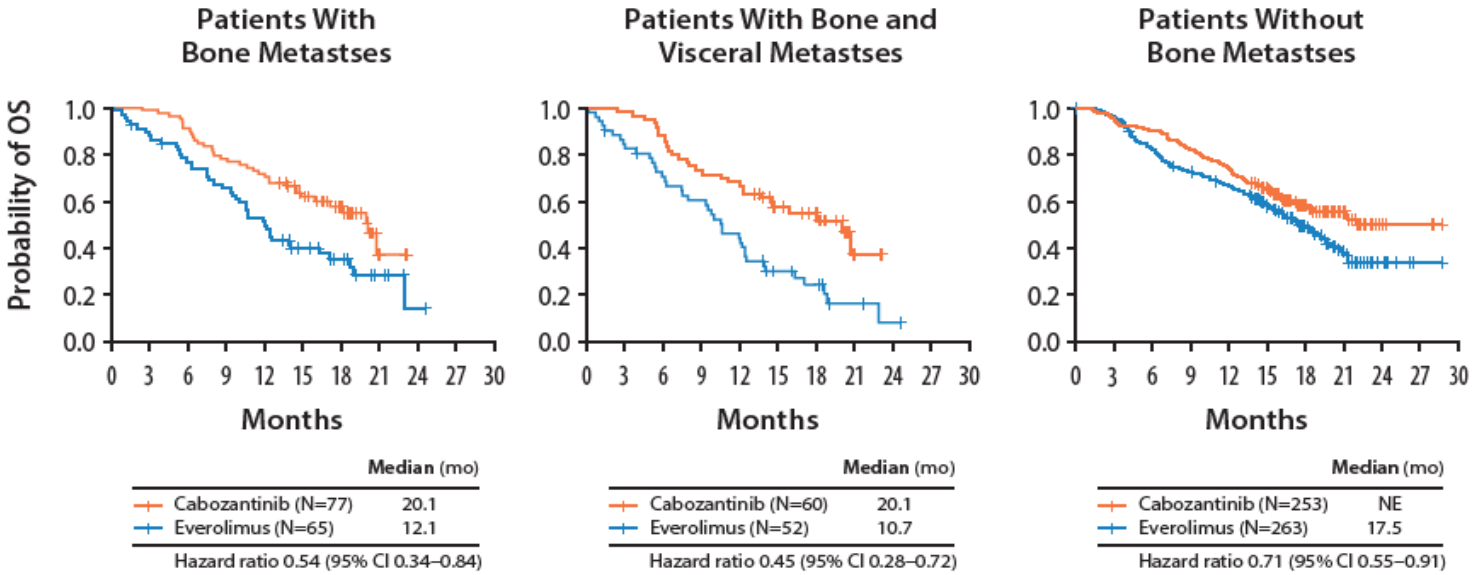
Choueiri TK et al. *Lancet Oncol.* 2016.

OVERALL SURVIVAL AND PFS IN SUBGROUPS



Choueiri TK et al. Lancet Oncol. 2016.

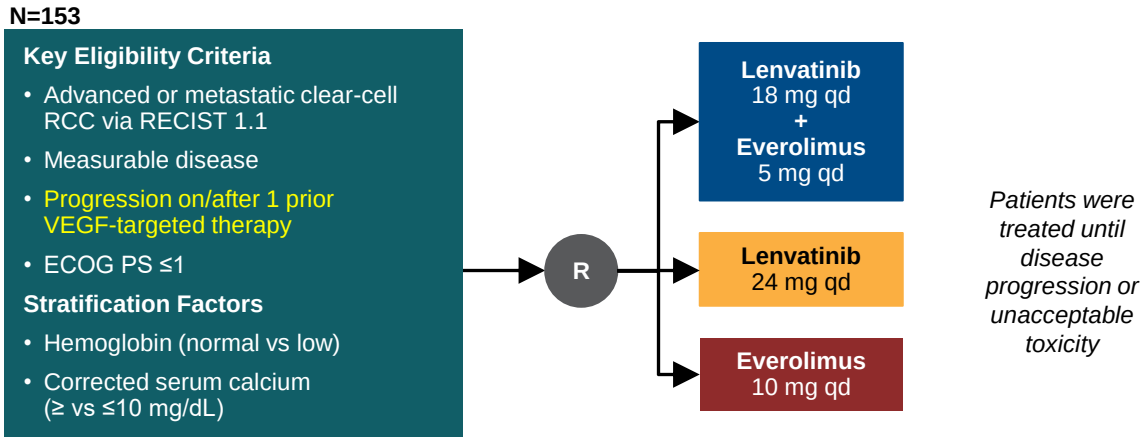
OVERALL SURVIVAL BY BONE METASTASES



Bone metastases status was based on the presence of bone metastases by CT or MRI per IRC at baseline.
NE, not estimable

Escudier B et al. *J Clin Oncol.* 2018.

STUDY 205: PHASE 2 TRIAL OF LENVATINIB ± EVEROLIMUS VS. EVEROLIMUS IN PREVIOUSLY TREATED METASTATIC RCC

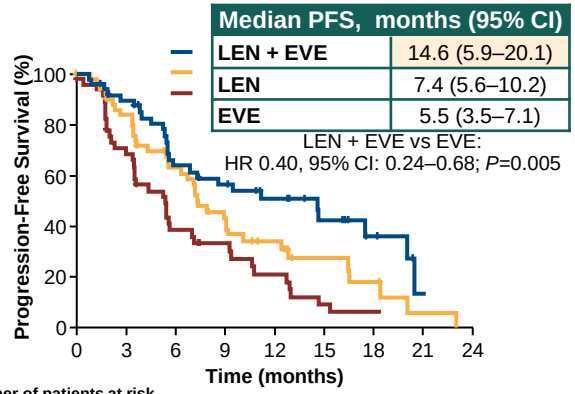


Primary Outcome Measure: PFS
Secondary Outcome Measures: Safety and tolerability, PK, OS, ORR

Motzer RJ et al. *Lancet Oncol.* 2015.

STUDY 205: RESPONSE, PFS, AND OS BENEFIT

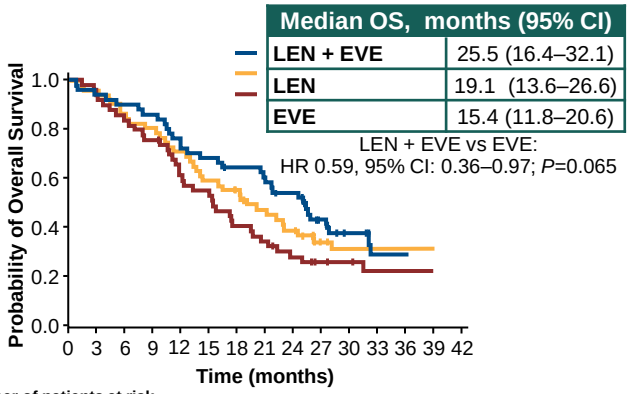
ORR*	LEN + EVE	LEN	EVE
Events	22 (43%)	14 (27%)	3 (6%)
95% CI	29–58	16–41	1–17
CR	1 (2%)	0	0



Adapted from Hutson e al. 2016.

Number of patients at risk

LEN + EVE	51	41	27	23	16	10	5	1	0
LEN	52	41	29	20	11	6	4	1	0
EVE	50	29	15	11	7	3	1	0	0



Number of patients at risk

LEN + EVE	51	48	46	44	37	35	32	30	26	17	11	7	2	0	0
LEN	52	50	45	42	37	31	28	23	19	12	7	3	2	1	0
EVE	50	46	42	38	30	27	20	17	13	10	9	5	1	0	0

Motzer RJ et al. *Lancet Oncol.* 2015 and Hutson T et al. ASCO 2016

Second-line Options in 2018

- Nivolumab
- Cabozantinib
- Axitinib
- Clinical Trial

Second-line Treatment

Started on Cabozantinib 60 mg daily

Side-effects:

- mild fatigue
- hypertension

Imaging:

- Stable bone metastases
- Regression of lung mets

Summary
“Favorable Risk” metastatic Clear-cell RCC Post TKI Options

- Nivolumab, cabozantinib and levantinib + everolimus are therapies that confer a significant OS benefit in pretreated (VEGF/R) patients

- Current options post first line TKI include cabozantinib, nivolumab and axitinib

Metastatic Renal Cell Carcinoma

Case Study on Sequencing Intermediate/Poor Risk Disease

Sebastien J Hotte, MD, FRCPC
Associate Professor of Oncology, McMaster University
Hamilton, Ontario

- 65 year old male
- Presented with hematuria
- Non smoker but severe kyphoscoliosis with COPD
- Hemoglobin 100; Calcium normal; KPS 70-80
- CT Scan - 13 cm renal mass into IVC; adrenal and lung mets – largest RUL 5.2cm

Int'l mRCC Database Consortium Prognostic Factors

KPS < 80%
Dx to Tx Interval <1yr
Anemia
Hypercalcemia
Neutrophilia
Thrombocytosis

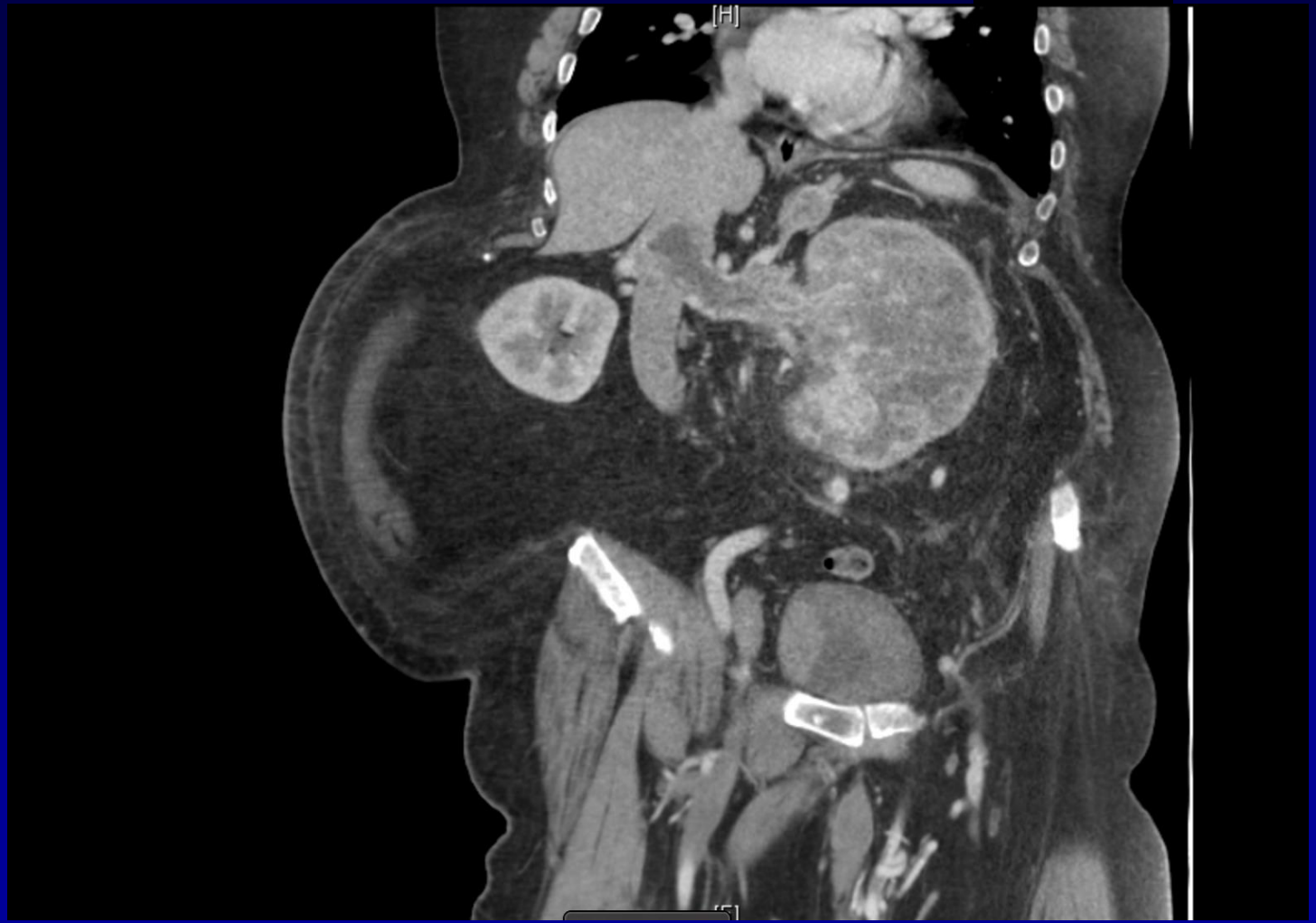
Heng et al J Clin Oncol 2009

Prognostic Factors

If patient has 0 factors:
Favorable Prognosis

If patient has 1-2 factors:
Intermediate Prognosis

If patient has 3-6 factors:
Poor Prognosis

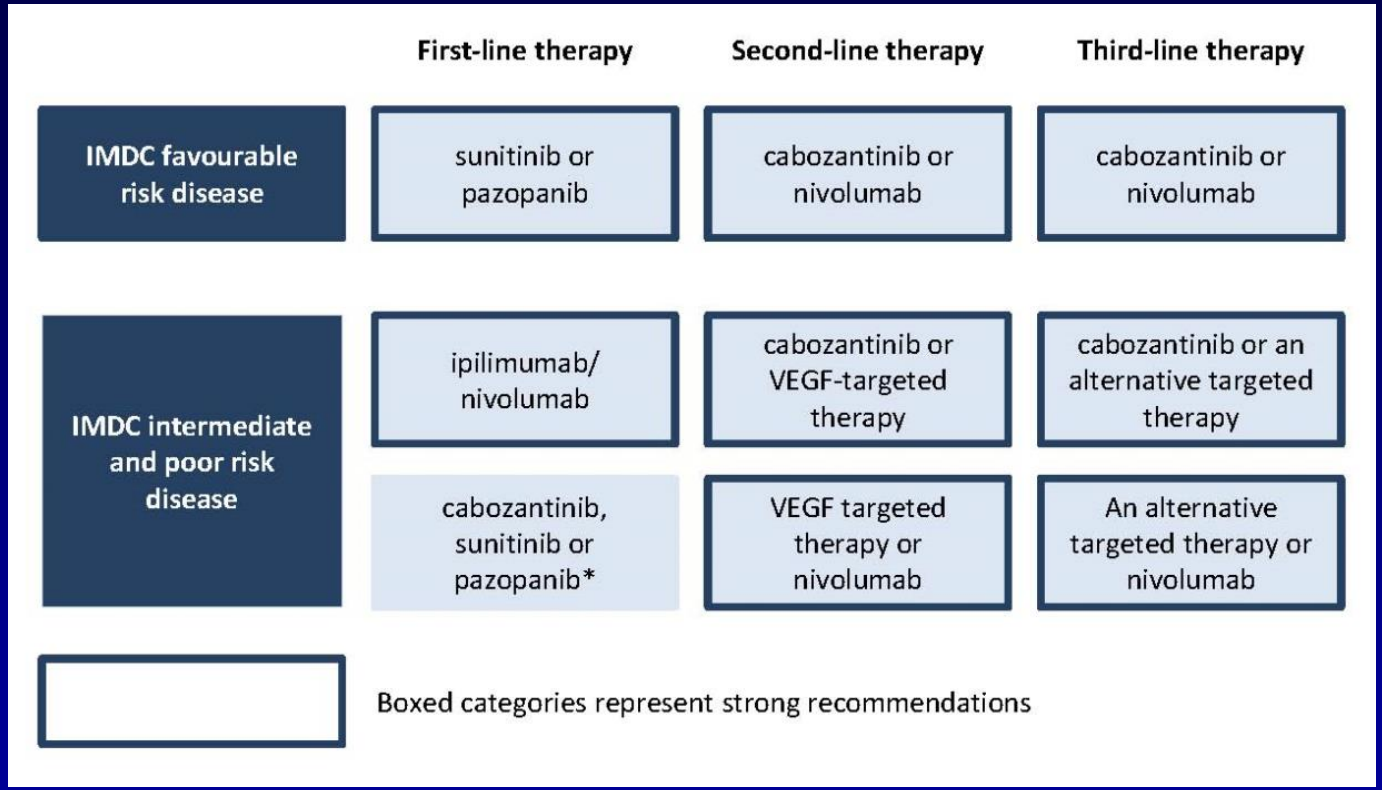

[H]

- Biopsy necessary ?
  - Lung biopsy: clear cell RCC, high grade
- Not a good surgical candidate
  - CARMENA – no role for CN, especially in intermediate/poor risk patients

First-line Options in Canada 2018

- Clinical trial
- Immunotherapy
  - Ipilimumab/Nivolumab
- VEGF targeted therapy
  - Sunitinib
  - Pazopanib

EAU 2018 Guidelines



IMDC=The International Metastatic Renal Cell Carcinoma Database Consortium;
VEGF=vascular endothelial growth factor.

***pazopanib for intermediate risk only.**

First-line

- Started on ipilimumab/nivolumab
  - Completed 4 cycles
    - Infusion reactions to nivolumab first 3 infusions
    - Otherwise minimal toxicity
- CT after 4 cycles, before start of maintenance nivolumab
  - New, necrotic mediastinal nodes
  - Largest lung mass stable, a few new ones
  - Primary slightly larger
  - ? New small, necrotic liver metastasis

Second-line Options in 2018

- Nivolumab maintenance
- Sunitinib/pazopanib
- Cabozantinib
- Axitinib
- Clinical Trial

Second-line Options in 2018

- Nivolumab maintenance
  - Feels well
  - Tolerated well
  - Keen to continue
  - Comorbidities might make TKI difficult
- Sunitinib/pazopanib
- Cabozantinib
- Axitinib
- Clinical Trial

Cleveland Clinic
Barts Cancer Institute

Clinical Outcome of Patients With Metastatic Renal Cell Carcinoma (mRCC) Progressing on Front-Line Immune-Oncology Based Combination (IO-COMBO) Regimens

Pedro C Barata[1], Alfonso Gomez de Liano[2], Prateek Mendiratta[1], Valerie Crolley[2], Bernadett Szabados[2],, Laura Wood[1], Kimberly D Allman[1], Beth Zanick[1], Allison J. Tyler[1], Allison Martin[1], Timothy D. Gilligan[1], Petros Grivas[1], Moshe C. Ornstein[1], Jorge A. Garcia[1], Thomas Powles[2], Brian I Rini[1]
1. Cleveland Clinic Taussig Cancer Institute, Cleveland, OH 2. Barts Cancer Institute, London, UK

Table 1:Baseline Patient and Disease Characteristics

Characteristics	N=33
IMDC Risk Group	Favorable: 9 (27) Intermediate: 17 (52) Poor: 7 (21)
Location of Metastases	Lung: 25 (76) Lymph Nodes: 17 (52) Bone: 10 (30) Liver: 7 (21) Locoregional: 7 (21)
Prior Nephrectomy	21 (64)
Number of Prior Systemic Therapies	0: 32 (97) 1: 1 (3)
IO-COMBO regimen	Atezolizumab/bevacizumab: 21 (64) Ipilimumab/nivolumab: 11 (33) Axitinib/avelumab: 1 (3)
Number of Subsequent Systemic Therapies	1: 100% 2: 36% 3+: 15%
First Subsequent Systemic Therapy (n=33)	Axitinib: 16 (48) Cabozantinib: 4 (12) Pazopanib: 9 (27) Sunitinib: 4 (12)
Second Subsequent Systemic Therapy (n=12)	Axitinib: 3 (25) Cabozantinib: 1(8) HIF inhibitor: 1 (8) Lenvatinib/everolimus: 1 (8) mTOR inhibitor: 1 (8) Nivolumab: 1 (8) Sorafenib: 1 (8) Sunitinib: 1 (8) Tivozanib: 2 (17)

hot

Table 2: Best Response to first subsequent treatment

Best Response (N=28)	N (%)
Objective Response Rate (ORR)	**8 (29)**
Complete Response (CR)	0 (0)
Partial Response (PR)	8 (29)
Stable Disease (SD)	15 (54)
Progressive Disease (PD)	5 (18)

Table 3: First Subsequent Treatment PFS

Treatment Characteristics and Outcomes (N = 33)		
Median PFS (n=33)	**6.4 months (4.4-8.4)**	
Median PFS – prior VEGF+IO (n=22)	6.2 months (5.2-7.2)	p=0.3
Median PFS – prior IO+IO (n=11)	7.6 months (3.6-11.6)	

ASCO 2018: J Clin Oncol 36, 2018 (suppl 6S; abstr 613)

Cleveland Clinic Taussig Cancer Institute

City of Hope

A prospective phase II multi-center study of individualized axitinib (Axi) titration for metastatic renal cell carcinoma (mRCC) after treatment with PD-1 / PD-L1 inhibitors

Moshe C. Ornstein[1], Sumanta K. Pal[2], Laura S. Wood[1], Kimberly D. Allman[1], Allison Martin[1], Jorge A. Garcia[1], Timothy D. Gilligan[1], Donna Company[1], Thomas Olencki[3], Kimryn Rathmell[4], Brian I. Rini[1]

[1]Cleveland Clinic Taussig Cancer Institute, Cleveland OH; [2]City of Hope Comprehensive Cancer Center, Duarte CA; [3]Ohio State James Comprehensive Cancer Center, Columbus OH; [4]Vandebilt-Ingram Cancer Center, Nashville TN

The James — The Ohio State University Comprehensive Cancer Center

Vanderbilt-Ingram Cancer Center

Results – Patient Characteristics

Male	29 (73%)
Age	64 (29 - 81)
KPS ≥80	36 (90%)
IMDC	
Favorable	4 (10%)
Intermediate	29 (73%)
Poor	7 (18%)
Number prior therapies	
1	11 (28%)
2	17 (43%)
3	11 (28%)
4	1 (3%)
Most recent therapy[1]	
Nivolumab	26 (65%)
Ipilimumab/Nivolumab	6 (15%)
Nivolumab/HIF inhibitor	3 (8%)
Atezolizumab	2 (5%)

[1]n=1 for Durvalumab/Tremelimumab, Durvalumab, Bevacizumab/Atezolizumab

Results – Clinical outcomes

Median PFS	**9.2 months**
ORR[1]	**39.5%**
PR	15 (39.5%)
SD	18 (43%)
PD	5 (13%)
6-month event-free survival rate	65%
1-year event-free survival rate	31%

[1] 38 patients evaluable for response

ASCO 2018: J Clin Oncol 36, 2018 (suppl; abstr 4517)

Activity of cabozantinib (cabo) after PD-1/PD-L1 immune checkpoint blockade (ICB) in metastatic clear cell renal cell carcinoma (mccRCC)

		Best Response to Cabo			
	N	**PR**	**SD**	**PD**	**Unevaluable**
All patients	69	23(33%)	32(46%)	12(17%)	2(3%)
By prior ICB type					
ICB alone	37	16(43%)	15(41%)	5(14%)	1(3%)
ICB+VEGF	24	6(25%)	12(50%)	5(21%)	1(4%)
ICB+Other	8	1(13%)	5(63%)	2(25%)	
By prior ICB duration					
<6mos	42	12(29%)	22(52%)	8(19%)	
>6mos	27	11(41%)	10(37%)	4(15%)	2(7%)

B.A. McGregor, A. Lalani, …, T.K. Choueiri. Annals of Oncology (2018) 29 (suppl_8): viii303-viii331. 10.1093/annonc/mdy283

SUMMARY
"INTERMEDIATE/POOR RISK " METASTATIC CLEAR-CELL RCC POST IPI/NIVO OPTIONS

- No level 1 evidence of most appropriate next line of therapy
  - –Will be difficult to generate as field moves on
- Biologically, no rationale for why any "first line" TKI would not work just as well
  - –Small prospective studies and retrospective series suggest this is the case
- No data on efficacy of IO re-challenge later in disease progression

Considerations of subsequent line therapy

- Patient level:
  - clinical status, comorbidities
  - disease characteristics, burden
  - experience on previous lines of therapy, A/E (irAE)
- Access to agents with unique mechanisms of action
  - efficacy (OS endpoint robust)
  - level of evidence, real world data
  - tolerability
  - cost, convenience

SOME ONGOING CLINICAL QUESTIONS:

1. Ideal sequence and optimization of agents with unique MOA?
2. Ongoing clinical trials to optimize/sequence treatment?
3. Can we stop an IO drug?
4. Re-defining appropriate clinical endpoints, response assessment, treatment beyond progression?

OPTIMAL SEQUENCE PD/PD-L1, CTLA-4 AND VEGF-TKI IN MRCC?

- Combinations IO/IO and VEGF inhibitors have higher ORR and higher toxicity than single agent IO…

- Can a sequential single agent approach lead to more optimization?
  - Less toxicity.
  - Same cumulative PFS (PFS1+PFS2), OS or potentially better (tumor priming?)

- Activity of agents after IO/IO or IO/VEGF?
  - Cabozantinib (n=86) = ORR 36%, TTF 6.5 mos (*McGregor, Lalani et al. ESMO 2018*)
  - Axitinib (dose-individualized, n=38) = ORR 39.5%, PFS 9.2 mos (*Ornstein et al. ASCO 2018*)

Summary

- Combination therapies with IO backbone are shaping our next wave of mRCC treatment options
- Treatment considerations in subsequent-line setting include disease characteristics, patient clinical status / experience on previous agents, access to lines of therapy with unique MOA
- Ultimately, we seek to maintain the remarkable recent progress in bringing more options to our RCC patients

Thank You!

Canadian Urological Association
The Voice of Urology in Canada

Association des urologues du Canada
La voix de l'urologie au Canada