Renal cell cancer: Old friends and new players

KOÇ ÜNİVERSİTESİ

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28.11.2019, Antalya

- Epidemiology
- Adjuvant systemic therapy
- 1. line systemic therapies in advanced cancer, new agents selected new combinations
- 2. line and systemic therapies in advanced cancer
- Nephrectomy and/or metastasectomy in advanced renal cancer
- Conclusion

- %3 of all adult malignancies, 7th most common cancer
- Men >women
- Related with smoking, obesity and hypertension
- Median age of diagnosis 65
- 5 year survival rate has improved with new treatment agents

- Around %20 of patients present with metastatic disease, and fewer than %5 have a solitary metastasis
- Around %30 of patients undergoing curative therapy experience disease recurrence

- The principal treatment options are;
  - Surgery (only known curative treatment for localized disease, and it also used for palliation in metastatic disease)
  - Thermal ablation(as an alternative treatment for small lesions in carefully selected patients who are not candidates for surgery)
  - Active surveillance
  - Radiation therapy (metastatic disease)
  - Immunotherapy (metastatic disease)
  - Molecular-targeted therapy (metastatic disease)

SYSTEMIC THERAPY FOR ADVANCED RCC EMA AND FDA REGULATORY APPROVED DRUGS

Approval	Agent	EMA and FDA Indications
1992	Intereukin-2	Metastatic
2005	Sorafenib	Advanced
2006	Sunitinib	Advanced
2007	Temsirolimus	Advanced
2009	Bevacizumab (+ IFN-α)	Metastatic
2009	Everolimus	After failure of sunitinib or sorafenib
2009	Pazopanib	Advanced
2012	Axitinib	Failure of prior systemic therapy
2015	Nivolumab	Failure of prior systemic therapy
2016	Cabozantinib	Failure of prior systemic therapy
2016	Lenvatinib plus everolimus	Failure of prior systemic therapy

ESMO

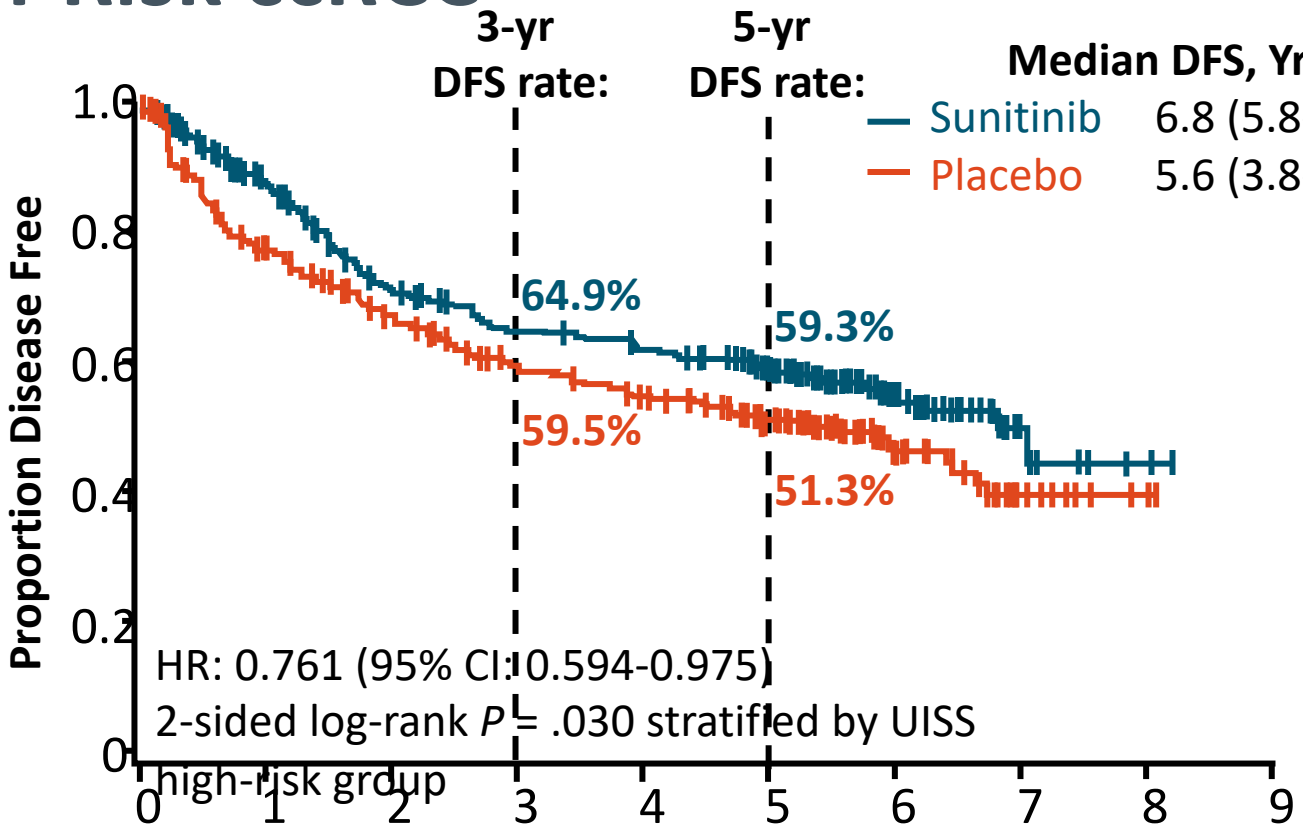
From ESMO guideline

Adjuvant studies

Recent adjuvant studies

- ASSURE study sunitinib/sorafenib/placebo
- PROTECT pazopanib/placebo
- S-TRAC sunitinib/placebo
  - The results showed benefit of sunitinib over placebo for DFS (p=0.03), but not for OS
  - Too much grade III-IV toxicities at sunitinib arm
- ATLAS study comparing axitinib/placebo did not meet its primary end point

S-TRAC Phase III Trial: DFS With Sunitinib vs Placebo in Patients With Locoregional, High-Risk ccRCC

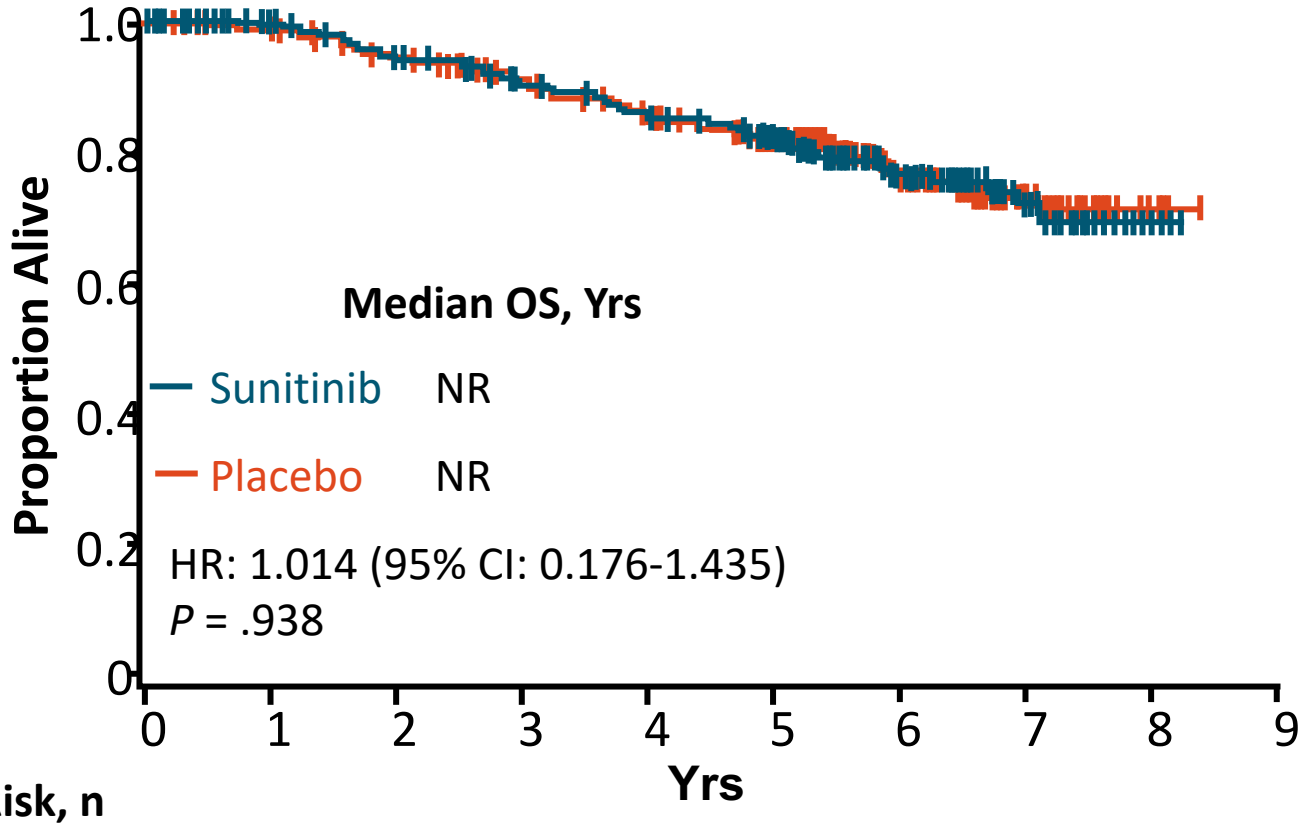


Patients at Risk, n

Sunitinib	309	225	173	153	144	119	53	10	3	0
Placebo	306	220	181	150	135	102	37	10	2	0

Ravaud. NEJM. 2016;375:2246.

S-TRAC Phase III Trial: OS With Sunitinib vs Placebo in Patients With Locoregional, High-Risk ccRCC



Patients at Risk, n

Sunitinib	309	278	258	236	222	196	98	31	4	0
Placebo	306	289	269	250	231	197	96	40	4	0

Ravaud. NEJM. 2016;375:2246.

Published Tyrosine Kinase Inhibitor Adjuvant Trials

Trial	Therapy	N	Histology	Stage	Starting Dose	Minimum Dose	DFS	OS
ASSURE[1]	Sunitinib Sorafenib Placebo	1943	**79% ccRCC**	> pT1b, G3-4, or N+	50 or 37.5 mg (Su)/ 400 mg (So)	25 mg (Su)/40 mg (So)	No	No
S-TRAC[2]	Sunitinib Placebo	615	ccRCC	> pT3b or N+	**50 mg**	**37.5 mg**	Yes	No
PROTECT[3]	Pazopanib Placebo	1538	ccRCC or mostly ccRCC	pT2 (G3-4), ≥ pT3, or N+	600 mg	400 mg	No	No

1. Haas. Lancet. 2016;387:2008. 2. Ravaud. NEJM. 2016;375:2246. 3. Motzer. JCO. 2017;35:3916.

Ongoing Phase III Adjuvant Trials: Immunotherapy vs Placebo

Parameter	IMmotion010[1] (NCT03024996)	PROSPER[2] (NCT03055013)	KEYNOTE-564[3] (NCT03142334)	CheckMate 914[4] (NCT03138512)
Drug	Atezolizumab	Nivolumab	Pembrolizumab	Nivolumab + ipilimumab
Histology	Clear-cell ± sarcomatoid histology	RCC of any histology	Clear-cell ± sarcomatoid features	Clear-cell ± sarcomatoid features
Dose duration	1 yr	2 doses prior to surgery and adjuvant nivolumab for 9 mos	1 yr	6 mos
Risk classification	T2 grade 4, T3a grade 3/4, T3b/c any grade, T4 any grade, or TxN+ any grade	Clinical stage ≥ T2 or any N+	pT2, grade 4; pT3/4, any grade; N+ M0; M1 NED	pT2aN0, grade 3-4; pT2b-T4; N+
Primary endpoint	DFS	RFS at 5 yrs	DFS	DFS
BICR	Yes	Yes	Yes	Yes
Status	Active, recruiting	Active, recruiting	Active, recruiting	Active, recruiting

1. Uzzo. ASCO 2017. Abstr TPS4598. 2. Harshman. ASCO 2018. Abstr TPS4597.
3. Choueiri. ASCO 2018. Abstr TPS4599. 4. Bex. ESMO 2018. Abstr 927TiP.

Conclusion

- There is currently a lack of proven benefit of adjuvant therapy with VEGFR-TKIs for patients with high risk RCC after nephrectomy, and due to it’s toxicities adjuvant sunitinib is not recommended now

First line systemic therapies

Systemic therapies for metastatic disease

- Until targeted therapies were introduced in 2006 the treatment was generally based on immunotherapies such as interferon -α (IFN-α) and interleukin-2 (IL-2)
- Stabilisation of the disease and prolonged survival
- Sunitinib, sorafenib, pazopanib, axitinib, tivozanib, cabozantinib, everolimus, temsirolimus, bevacizumab+ IFN-α

What Does the Patient Want at Initial Presentation?

1. Cured of disease, preferably with limited toxicity during/after therapy and the ability to stop therapy

2. To live longer

3a. Disease control

3b. Quality of life maintained

FIRST-LINE TREATMENT OF RCC: OVERVIEW OF PIVOTAL TRIALS LEADING TO APPROVAL

Study	n	Response *vs.* IFN-α, %	Median Progression-free Survival *vs.* IFN-α, mo	Median Overall Survival *vs.* IFN-α, mo
Sunitinib *vs.* IFN-α[1]	750	47 *vs.* 12	11 *vs.* 5 P <0.01	26.4 *vs.* 21.8 P = 0.051
Bevacizumab + IFN-α *vs.* IFN-α[2]	649	31 *vs.* 12	10.4 *vs.* 5.5 P <0.01	23.3 *vs.* 21.3 P = 0.1291
Pazopanib *vs.* placebo[3]	233	30 *vs.* 3	11.1 *vs.* 2.8 P <0.01	NA
Temsirolimus *vs.* IFN-α[4] (Poor Risk)	626	9 *vs.* 5	5.5 *vs.* 3.1 P <0.01	10.9 *vs.* 7.3 P < 0.01

1. Motzer RJ, *et al.* J Clin Oncol 2009;27:3584-3590; 2. Escudier B, *et al.* J Clin Oncol 2009;27:1280-1289;
3. Sternberg CN, *et al.* J Clin Oncol 2010;28:1061-1068; 4. Hudes G, *et al.* N Engl J Med 2007;356:2271-2281

NCCN 2017

Predominant clear cell histology

Relapse or Stage IV and surgically unresectable

FIRST-LINE THERAPY
(alphabetical by category and preference)

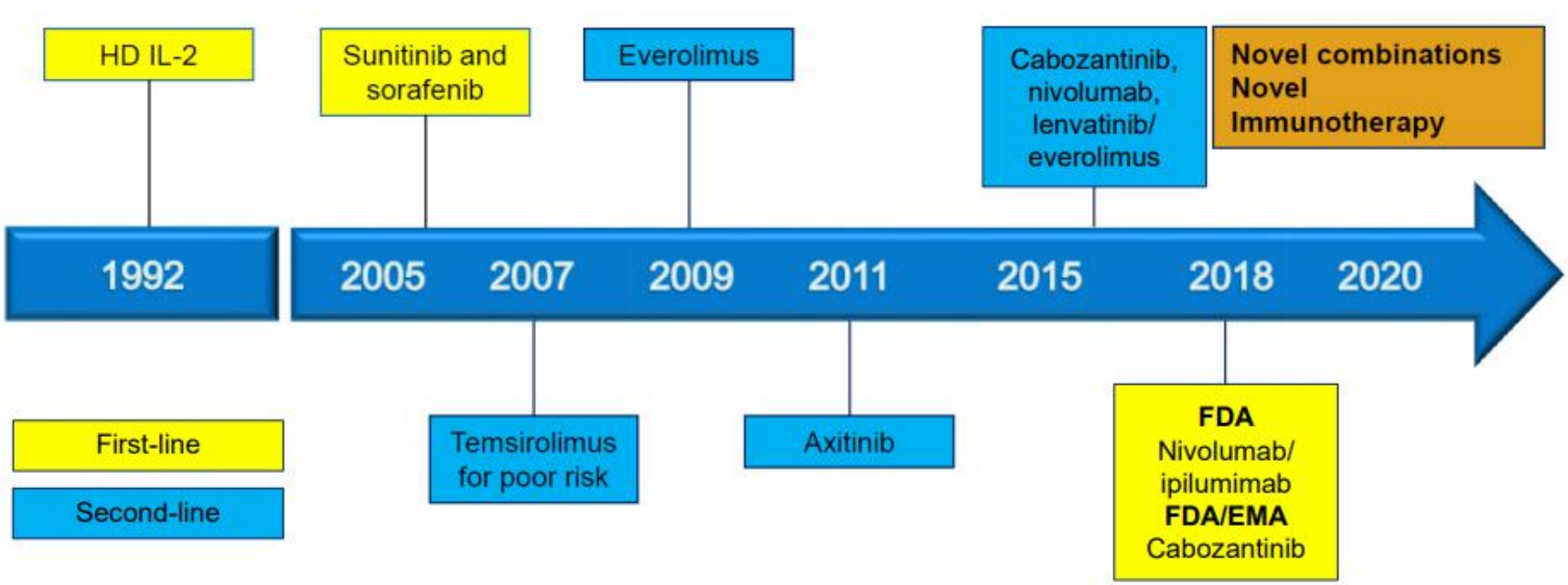
Clinical trial
or
Pazopanib (category 1, preferred)
or
Sunitinib (category 1, preferred)
or
Bevacizumab + IFN (category 1)
or
Temsirolimus (category 1 for poor-prognosis patients,[f] category 2B for selected patients of other risk groups)
or
Axitinib
or
High-dose IL-2 for selected patients[g]
or
Sorafenib for selected patients

and
Best supportive care.[h]
See NCCN Guidelines for Palliative Care

	N	Median PFS (95% CI)
Pazopanib	557	8.4 mo (8.3, 10.9)
Sunitinib	553	9.5 mo (8.3, 11.1)
HR (95% CI) = 1.047 (0.898,1.220)		

The upper bound of 95% CI hazard ratio <1.25 indicates pazopanib is non-inferior compared to sunitinib

Increasing Treatment Options in RCC



EMA, European Medicines Agency; FDA, [United States] Food & Drug Administration; HD IL-2, high-dose interleukin-2

Pal SK, et al. Presented at: 2018 Genitourinary Cancers Symposium; February 8-10, 2018: San Francisco, California, United States. Abstract 584.

Randomized Phase III Study Designs for Combination Tx

IMmotion151[1]

Treatment-naive advanced or metastatic RCC with clear-cell and/or sarcomatoid histology; KPS ≥ 70; tumor tissue available for PD-L1 staining
(N = 915)

- **Atezolizumab** 1200 mg IV + **Bevacizumab** 15 mg/kg IV Q3W
- **Sunitinib** 50 mg PO QD for 4 wks on, 2 wks off

1º EP: PFS in PD-L1+ pts; OS in ITT pts

JAVELIN Renal 101[2]

Treatment-naive advanced RCC with a clear-cell component;
ECOG PS 0 or 1; tumor tissue for PD-L1 staining
(N = 886)

- **Avelumab** 10 mg/kg IV Q2W + **Axitinib** 5 mg PO BID in 6-wk cycles
- **Sunitinib** 50 mg PO QD for 4 wks on, 2 wks off

1º EP: PFS and OS in PD-L1+ pts

KEYNOTE-426[3]

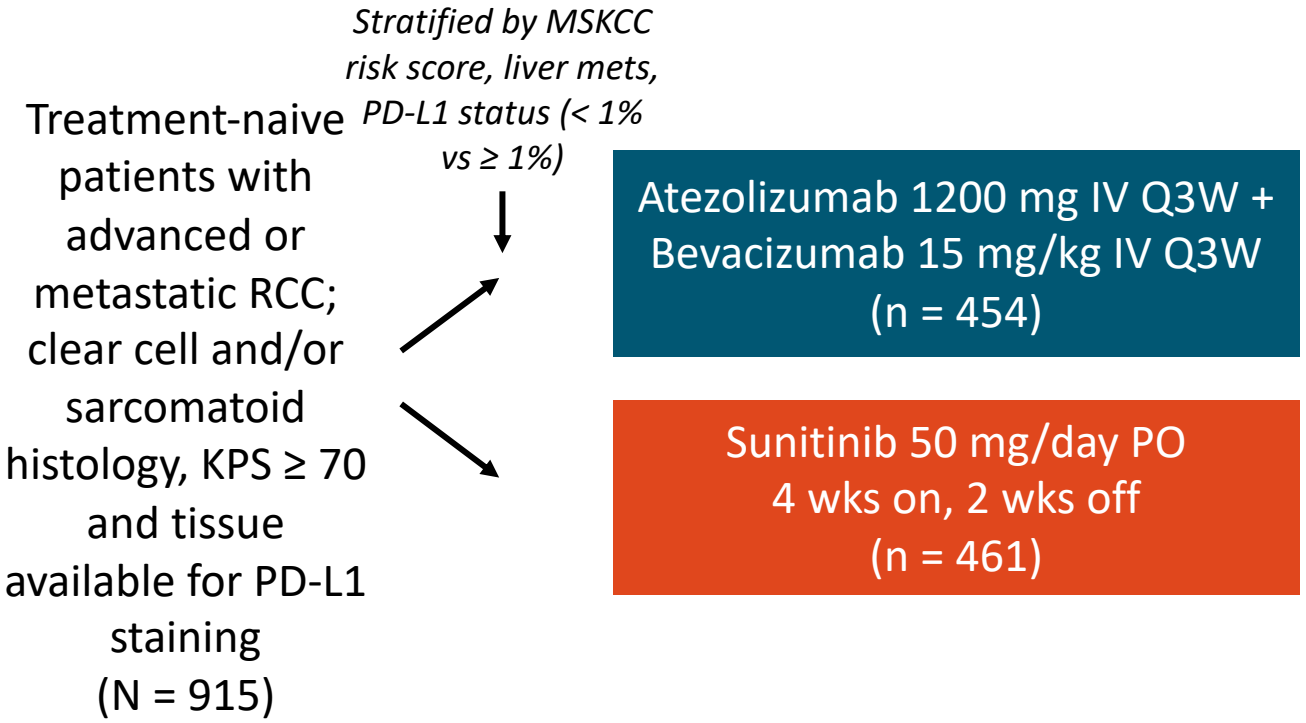
Patients with treatment-naive advanced clear-cell RCC; KPS ≥ 70%; tumor tissue for PD-L1 staining
(N = 861)

- **Pembrolizumab** 200 mg IV Q3W + **Axitinib** 5 mg PO BID
- **Sunitinib** 50 mg PO QD for 4 wks on, 2 wks off

1º EP: PFS and OS in ITT

1. Motzer. Genitourinary Cancers Symposium 2018. Abstr 578. 2. Motzer. ESMO 2018. Abstract LBA6. 3. Powles. Genitourinary Cancers Symposium 2019. Abstr 543.

IMmotion 151: Study Design

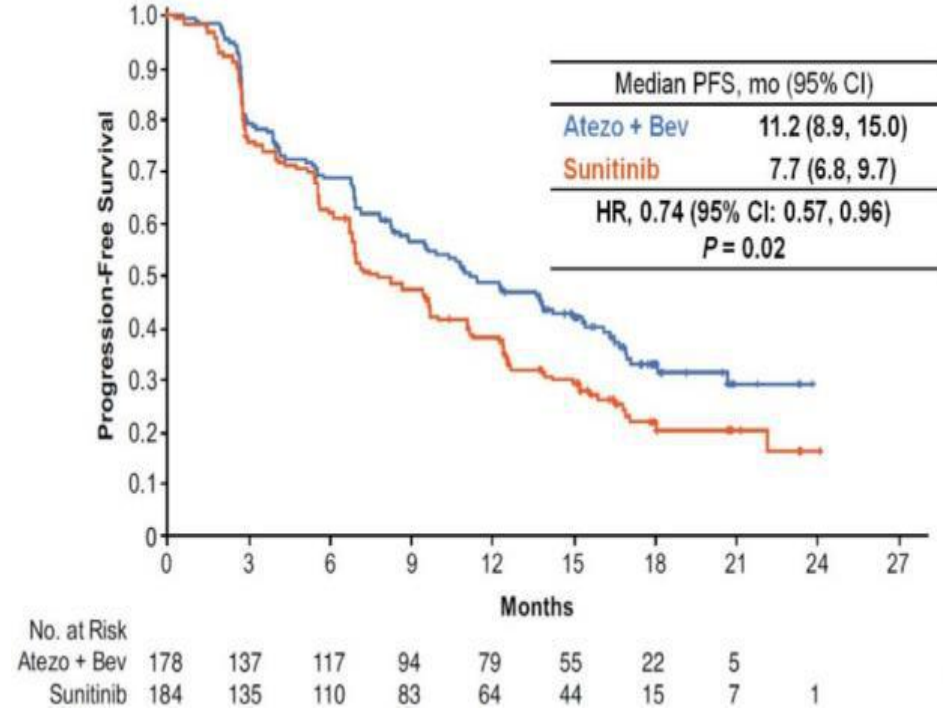


- Primary endpoints: PFS by PD-L1 status, OS in ITT
- Secondary endpoints: PFS in ITT, OS by PD-L1 status, ORR, patient-reported outcomes, safety

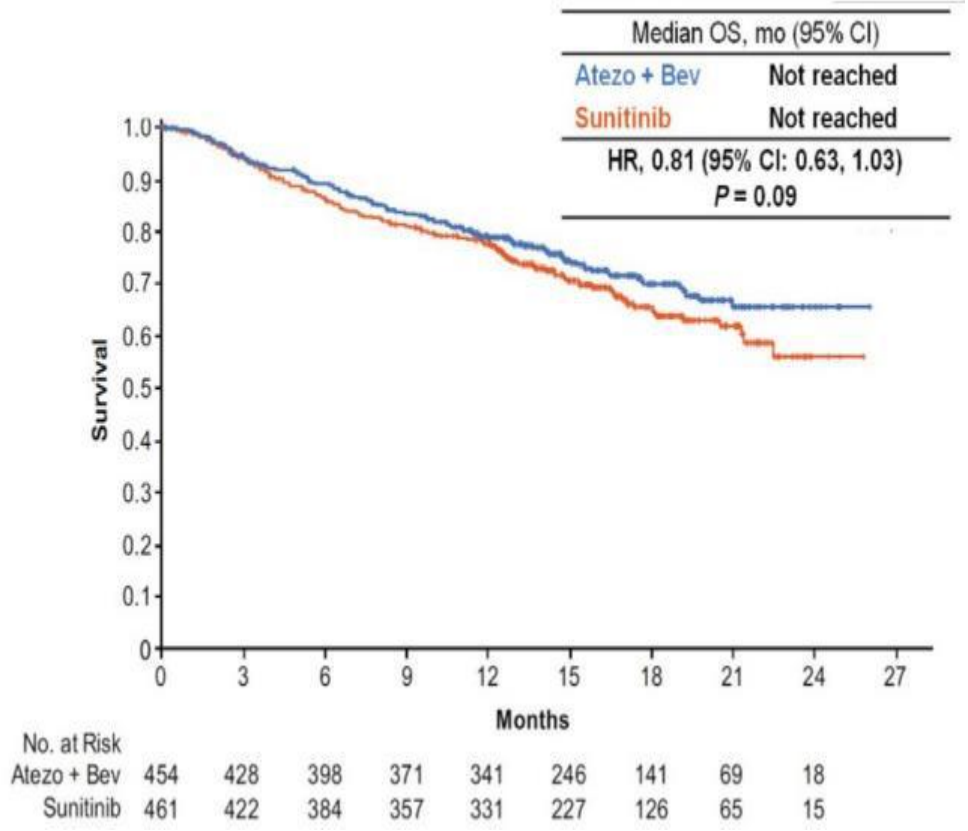
Motzer R, et al. ASCO GU 2018. Abstract 578. Escudier B, et al. ASCO 2018. Abstract 4511.

IMmotion151: Atezolizumab + Bevacizumab in Treatment-Naive Advanced RCC

PFS in PD-L1+ Cohort



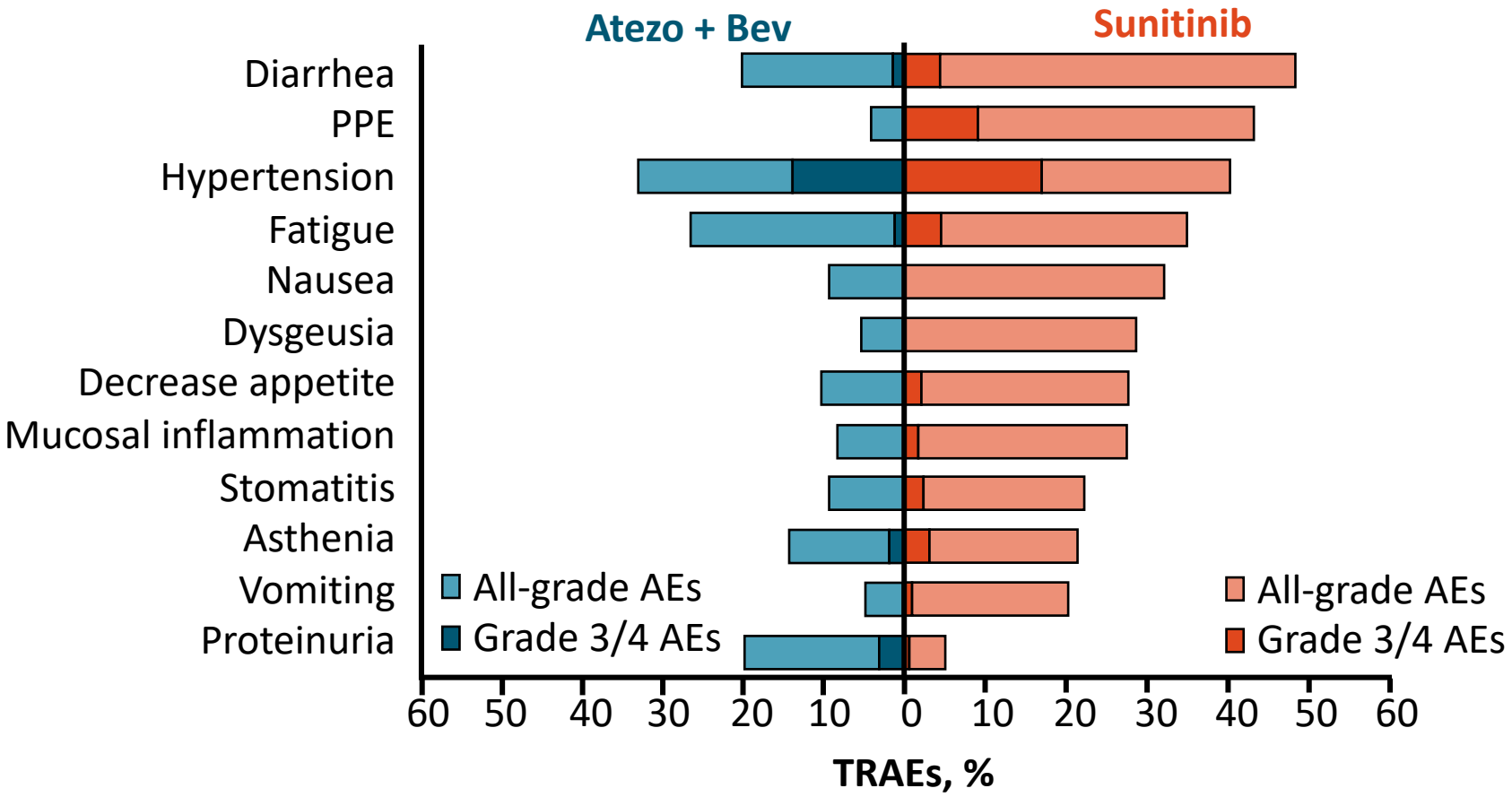
OS in ITT Cohort



Motzer. Genitourinary Cancers Symposium 2018. Abstr 578.

IMmotion151: TRAEs With Atezolizumab + Bevacizumab

Treatment-Related AEs in ≥ 20% of Either Arm and > 5% Difference Between Arms



Motzer. Genitourinary Cancers Symposium 2018. Abstr 578.

First-Line Checkpoint Inhibitor + TKI: Study Design

JAVELIN Renal 101

Key eligibility criteria:
- Treatment-naïve aRCC with a clear cell component
- ≥1 measurable lesion as defined by RECIST v1.1
- Tumor tissue available for PD-L1 staining
- ECOG PS 0 or 1

Stratification:
- ECOG PS (0 vs 1)
- Geographic region (USA vs Canada/Western Europe vs ROW)

N = 886

R 1:1

- Avelumab 10 mg/kg IV q 2 w + Axitinib 5 mg PO bid (6-week cycle)
- Sunitinib 50 mg PO qd (4 weeks on, 2 weeks off)

PRESS RELEASE

AVELUMAB PLUS AXITINIB SIGNIFICANTLY IMPROVED PROGRESSION-FREE SURVIVAL IN PREVIOUSLU UNTREATED PATIENTS WITH ADVACNED RENAL CELL CARCINOMA IN PHASE III STUDY

September 11, 2018

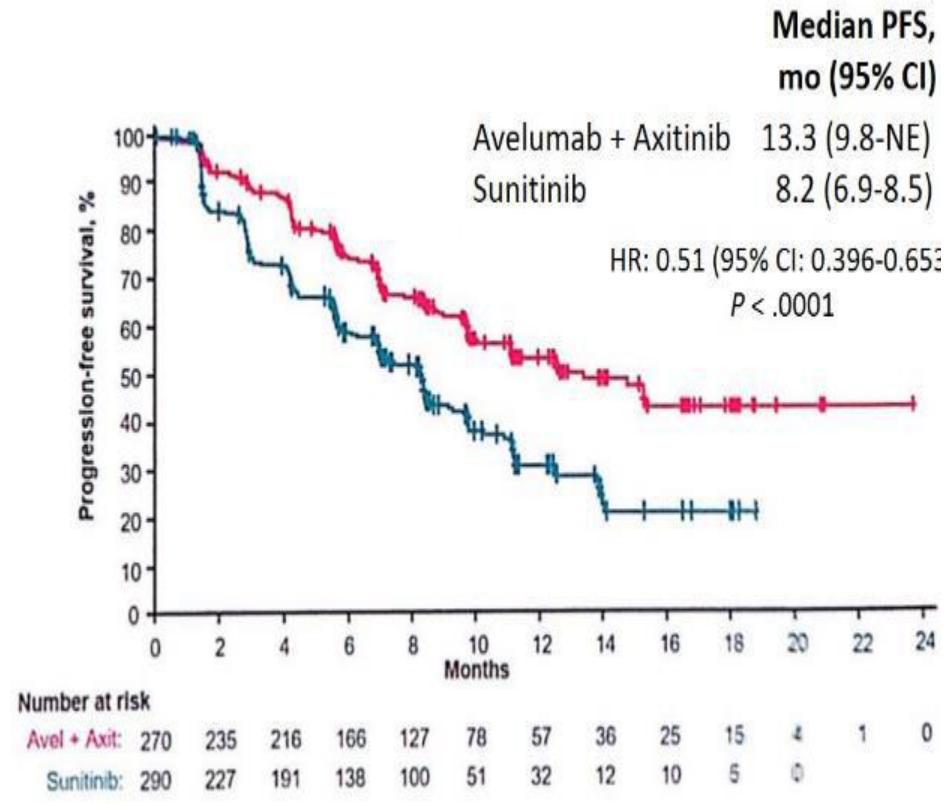
- First positive Phase III immunotherapy trial in combination with a tyrosine kinase inhibitor (TKI) in any tumor type
- Results significant in both PDL1+ and all-comer populations
- Alliance plans to pursue a regulatory submission in the US and discussions with other health authorities based on interim results for progression-free survival
- Trial will continue for the other primary endpoint of overall survival; detailed results to be submitted for presentation at an upcoming medical congress

BID, twice per day; IV, intravenous; PO, orally; ROW, rest of the world

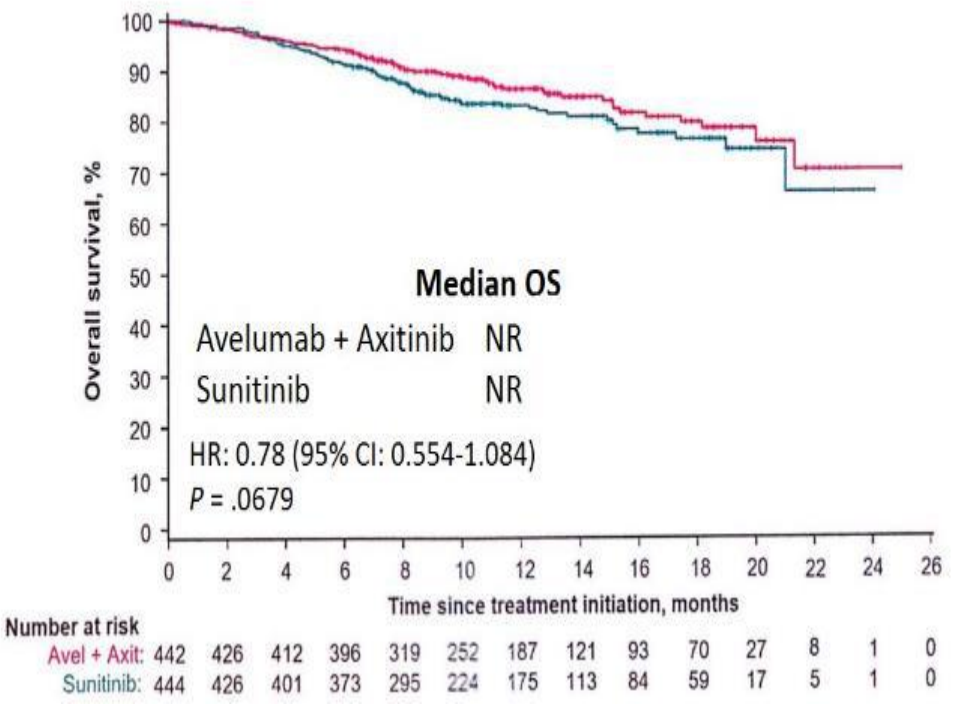
Motzer RJ, et al. *Ann Oncol.* 2018;29(Suppl 8): Abstract LBA6.

JAVELIN Renal 101: Avelumab + Axitinib in Treatment-Naive Advanced RCC

PFS in PD-L1+ Cohort



OS in ITT Cohort (Data Immature)



Motzer. ESMO 2018. Abstract LBA6.

JAVELIN Renal 101: TRAEs for Avelumab + Axitinib

Event, %	Avelumab + Axitinib (n = 434)		Sunitinib (n = 439)	
	All Grades	Grade 3 / 4	All Grades	Grade 3 / 4
TRAEs of any grade in ≥ 20% of pts or grade 3-4 in ≥ 3% of pts	95	51 / 4	96	48 / 7
▪ Diarrhea	54	5 / 0	45	3 / 0
▪ Hypertension	48	24 / 0	32	15 / 0
▪ Fatigue	36	3 / 0	36	4 / 0
▪ Hand-foot syndrome	33	6 / 0	34	4 / 0
▪ Dysphonia	27	1 / 0	3	0 / 0
▪ Nausea	25	1 / 0	34	1 / 0
▪ Hypothyroidism	24	< 1 / 0	13	< 1 / 0
▪ Stomatitis	22	2 / 0	23	1 / 0
▪ Decreased appetite	20	2 / 0	26	1 / 0
▪ Dysgeusia	13	0 / 0	32	0 / 0
▪ Increased alanine aminotransferase	13	4 / 1	10	2 / 0
▪ Thrombocytopenia	3	< 1 / 0	18	5 / 1
▪ Anemia	2	< 1 / 0	17	5 / < 1
▪ Neutropenia	1	< 1 / 0	18	7 / 1
TRAEs leading to discontinuation*	4		8	
TRAEs leading to death†	1		< 1	

Motzer. ESMO 2018. Abstract LBA6.

*No AEs observed in ≥ 1% of patients. †Grade 5 AEs: avelumab + axitinib, n = 3 (1 each of myocarditis, necrotizing pancreatitis, sudden death); sunitinib, n = 1 (intestinal perforation).

KEYNOTE-426 Study Design

Key Eligibility Criteria

- Newly diagnosed or recurrent stage IV clear-cell RCC
- No previous systemic treatment for advanced disease
- Karnofsky performance status ≥70
- Measurable disease per RECIST v1.1
- Provision of a tumor sample for biomarker assessment
- Adequate organ function

Stratification Factors

- IMDC risk group (favorable vs intermediate vs poor)
- Geographic region (North America vs Western Europe vs ROW)

R (1:1)

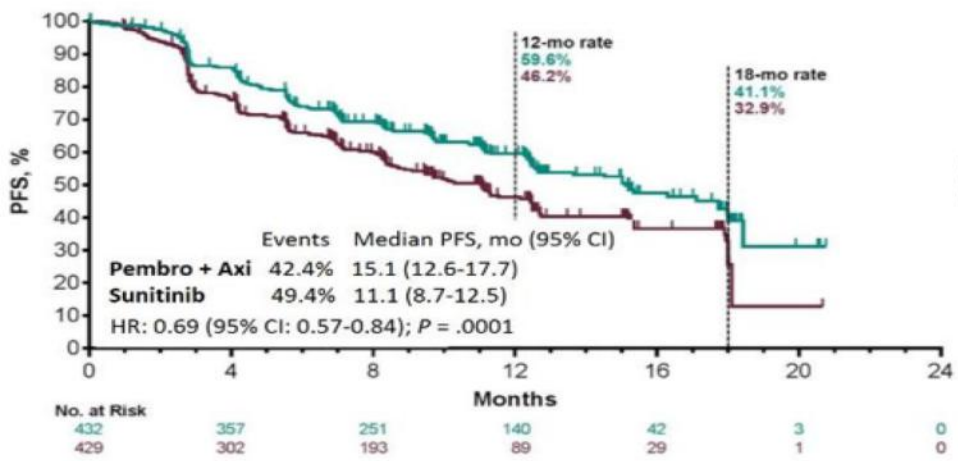
N = 432 → Pembrolizumab 200 mg IV Q3W for up to 35 cycles + Axitinib 5 mg orally twice daily[a]

N = 429 → Sunitinib 50 mg orally once daily for first 4 wks of each 6-wk cycle[b]

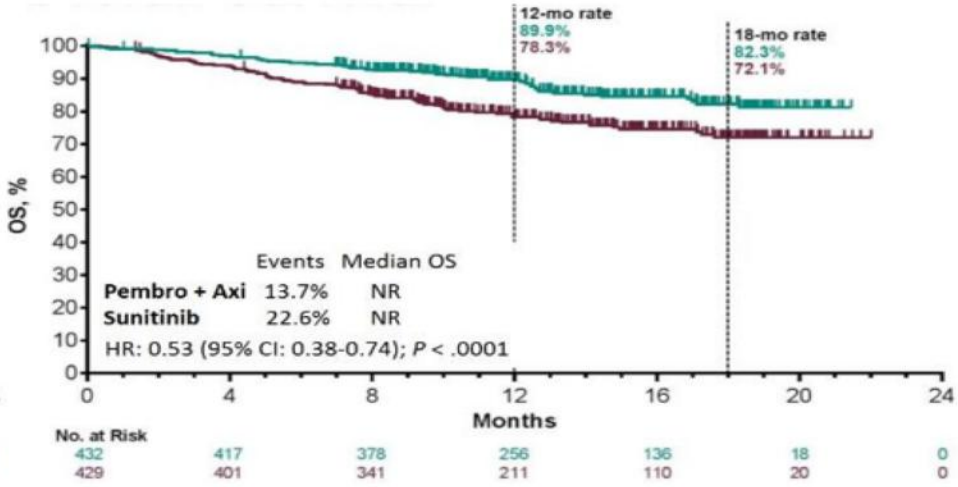
End Points

- **Dual primary:** OS and PFS (RECIST v1.1, BICR) in ITT
- **Key secondary:** ORR (RECIST v1.1, BICR) in ITT
- **Other secondary:** DOR (RECIST v1.1), PROs, safety

PFS in ITT Population

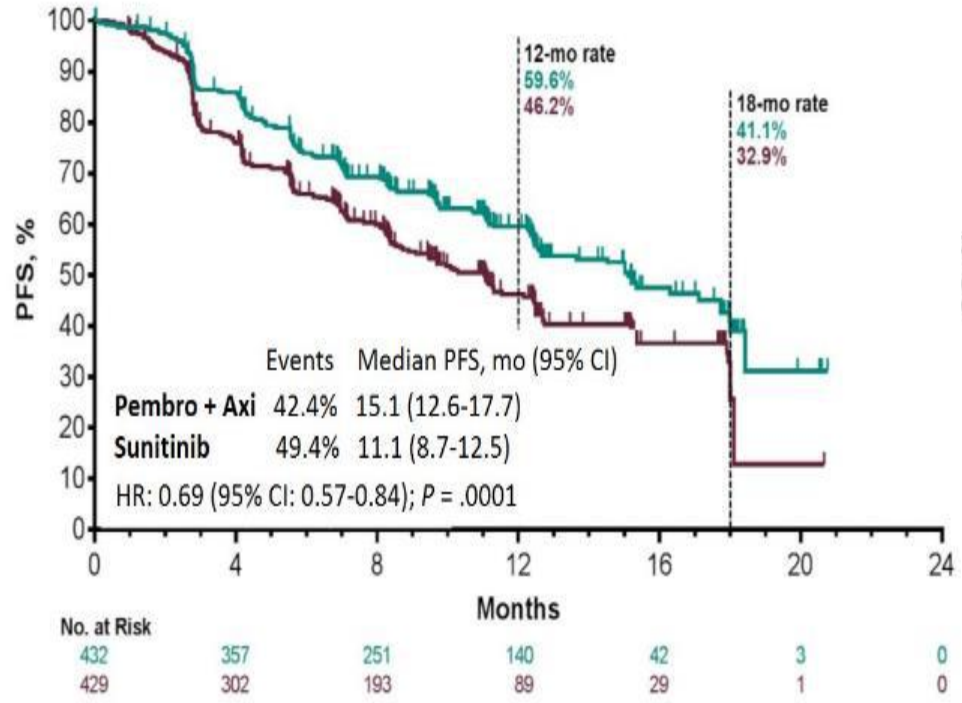


OS in ITT Population

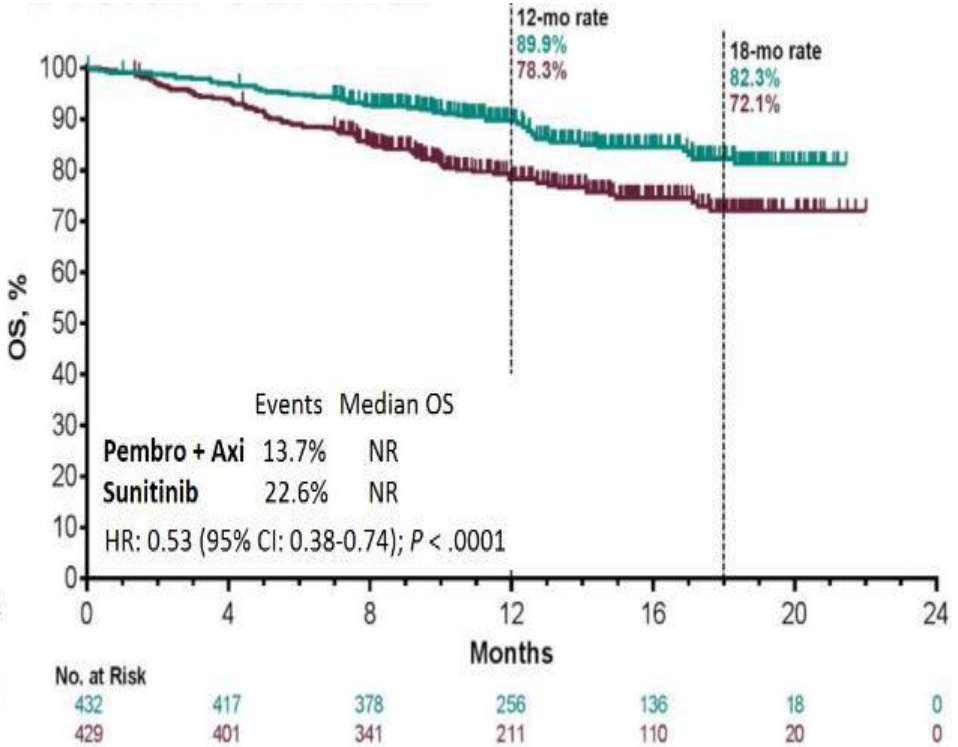


KEYNOTE-426: Pembrolizumab + Axitinib in Treatment-Naive Advanced RCC

PFS in ITT Population



OS in ITT Population



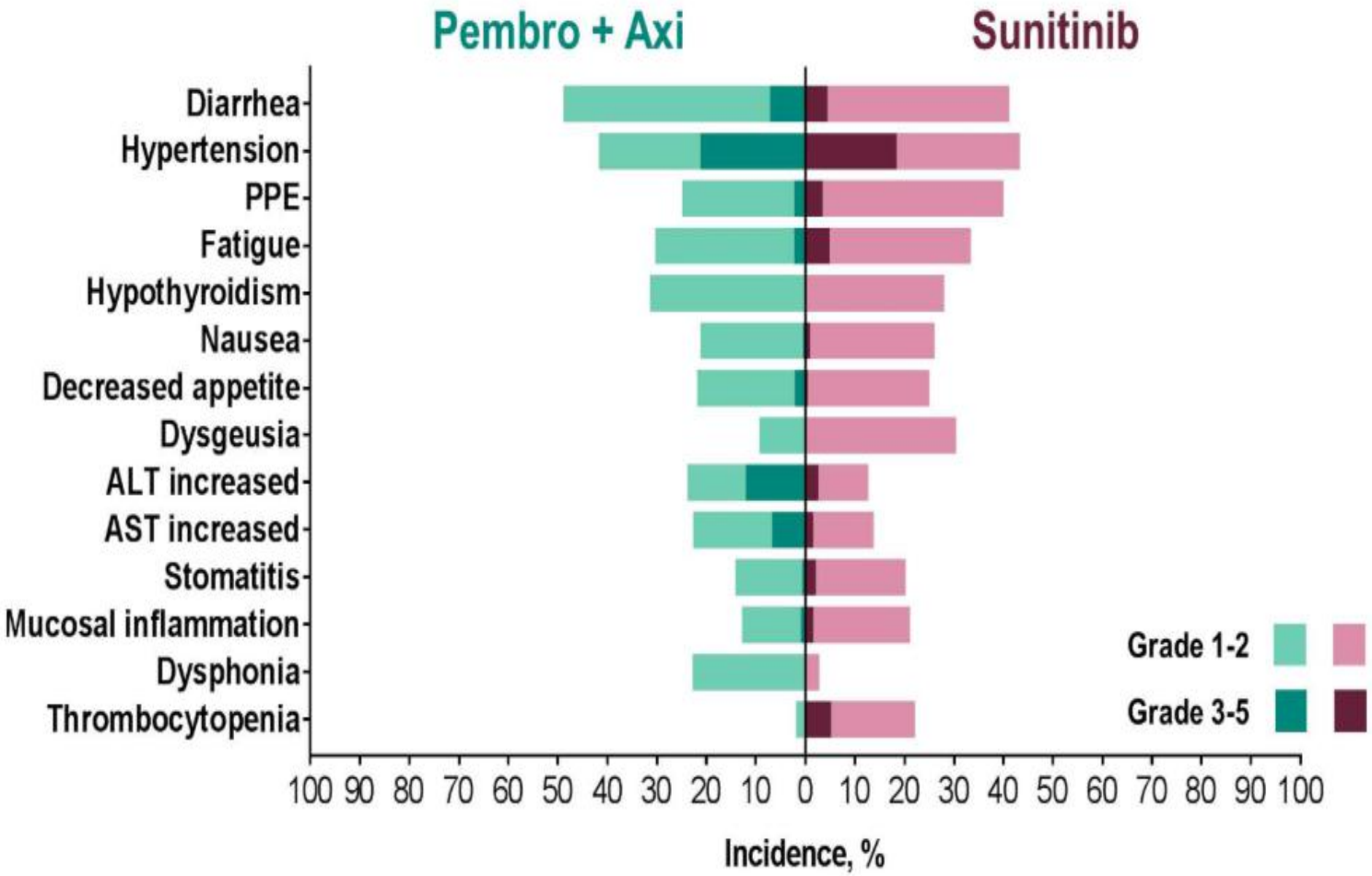
UPDATED AT ASCO GU 2019.

Powles. Genitourinary Cancers Symposium 2019. Abstr 543.

Slide credit: clinicaloptions.com

KEYNOTE-426: TRAEs With Pembro + Axi

Treatment-Related AEs in ≥ 20% of Either Arm



UPDATED AT ASCO GU 2019.

Powles. Genitourinary Cancers Symposium 2019. Abstr 543.

CHECKMATE 214

Nivolumab + ipilimumab *versus* sunitinib for first-line treatment in metastatic RCC

- Treatment-naïve advanced or metastatic clear-cell RCC
- Measurable disease
- Tumour tissue available for PD-L1 testing

Stratified by:

- IMDC prognostic score (0 *vs.* 1-2 *vs.* 3-6)
- Region (US *vs.* Canada/Europe *vs.* Rest of World) (N=1096)

RANDOMISATION

1:1

Nivolumab 3 mg/kg IV + ipilimumab 1 mg/kg IV 3QW for four doses, then nivolumab 3 mg/kg IV Q2W

Sunitinib 50 mg orally once daily for 4 weeks (6-week cycles)

Treatment until progression or unacceptable toxicity

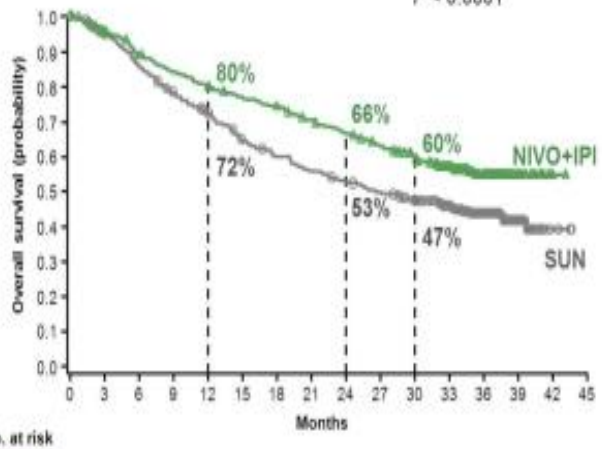
Intermediate- and poor-risk

Median OS, months (95% CI)

NIVO+IPI	NR (35.6–NE)
SUN	26.6 (22.1–33.4)

HR (95% CI), 0.66 (0.54–0.80)

P < 0.0001

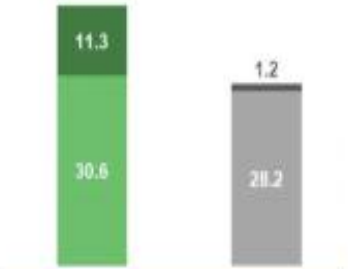


No. at risk

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

P = 0.0001

42% **ORR** 29%



Intermediate/poor risk[1]

NIVO+IPI N = 425	SUN N = 422
52	28

DOR >18 mos

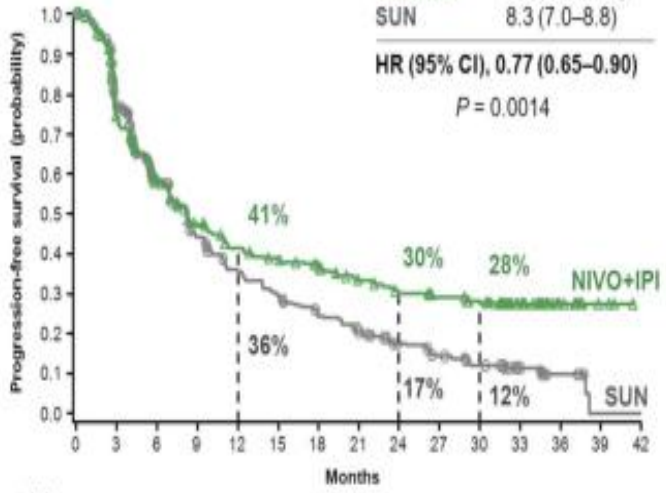
Intermediate- and poor-risk

Median PFS, months (95% CI)

NIVO+IPI	8.2 (6.9–10.0)
SUN	8.3 (7.0–8.8)

HR (95% CI), 0.77 (0.65–0.90)

P = 0.0014

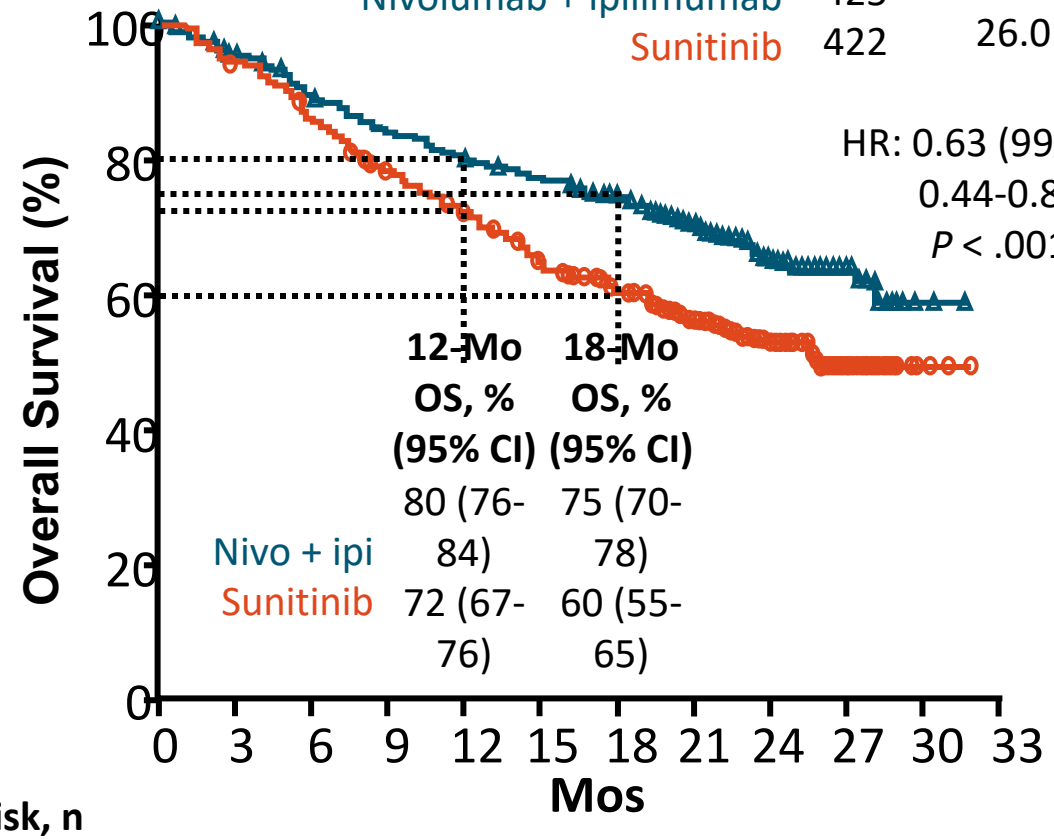


No. at risk

NIVO+IPI	425	296	218	173	147	135	125	106	95	87	81	48	17	3	0
SUN	422	295	200	142	111	93	75	60	44	34	26	16	6	0	0

Motzer RJ, et al. *N Engl J Med* 2018;378:1277-90; Motzer RJ, et al. *Lancet Oncol* 2019 Aug 16. pii: S1470-2045(19)30413-9. doi: 10.1016/S1470-2045(19)30413-9. [Epub ahead of print].

CheckMate 214: IMDC Intermediate-/Poor-Risk Patients Live Longer



Patients at Risk, n

Nivolumab + ipilimumab	425	399	372	348	332	318	300	241	119	44	2	0
Sunitinib	422	387	352	315	288	253	225	179	89	34	3	0

Motzer. NEJM. 2018;378:1277.

Phase III IO-Based Combinations in RCC

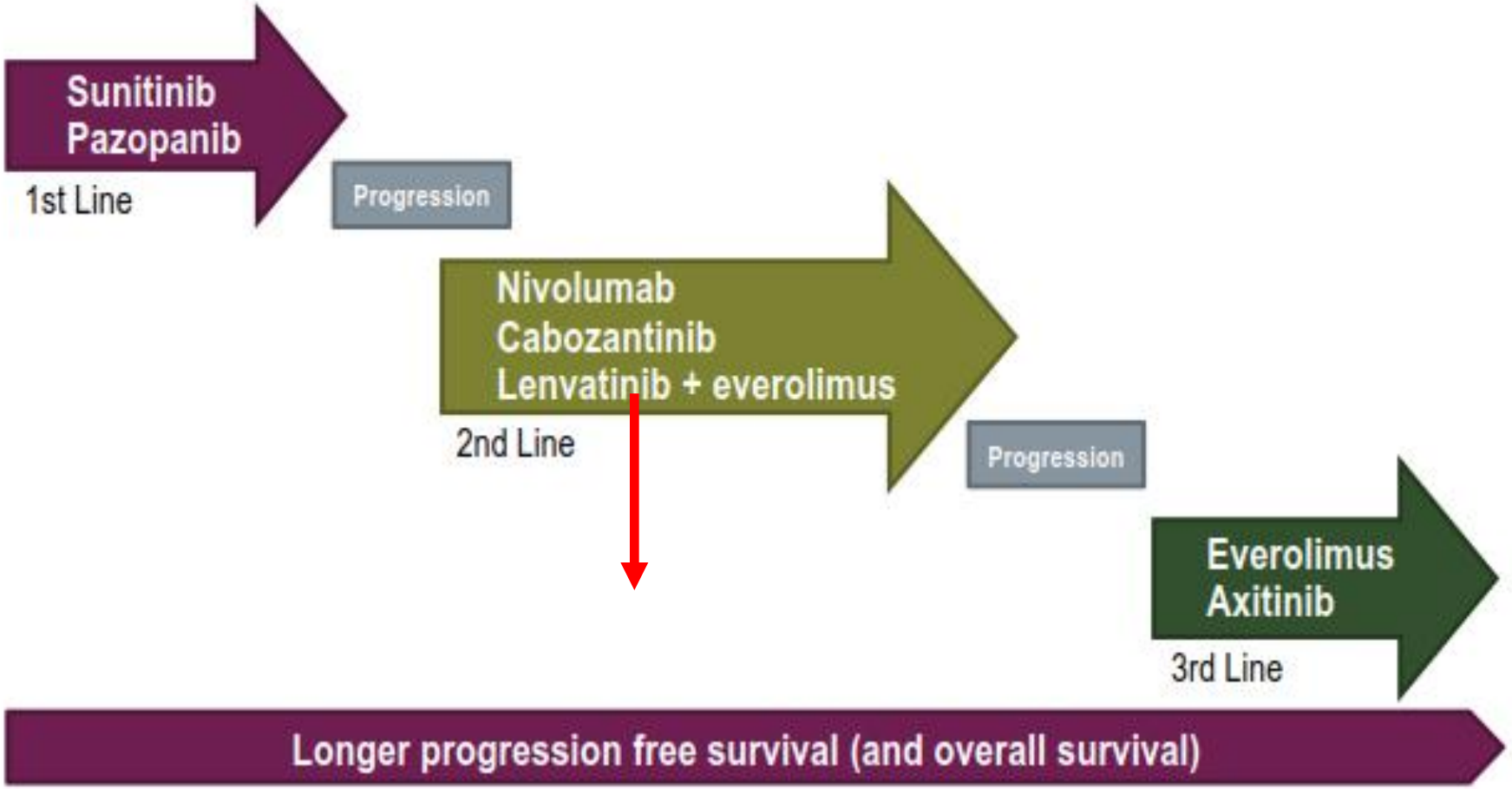
Control	Comparator(s)	PFS (HR)	OS (HR)	
Sunitinib	Nivolumab/ipilimumab[1]	No* (0.98)	Yes (0.68)	CM214
Sunitinib	Bevacizumab + atezolizumab[2]	Yes (0.83)	No (0.81)	IMmotion
Sunitinib	Axitinib + avelumab[3]	Yes (0.69)	No (0.78)	Javelin
Sunitinib	Axitinib + pembrolizumab[4]	Yes (0.69)	Yes (0.53)	KN 426
Sunitinib	Lenvatinib + everolimus *vs* lenvatinib/pembro	Pending	Pending	
Sunitinib	Cabozantinib/nivolumab	Pending	Pending	

1. Motzer. NEJM. 2018;378:1277. 2. Motzer. Genitourinary Cancers Symposium 2018. Abstr 578.
3. Motzer. ESMO 2018. Abstract LBA6. 4. Powels. Genitourinary Cancers Symposium 2019. Abstr 543.

Control Disease Rates for Major Regimens in mRCC

Regimen	Study	Median PFS, Mos	Primary PD Rate, %
Nivolumab + ipilimumab	CheckMate 214 (intermediate/poor risk)[1]	11.6	20
Atezolizumab + bevacizumab	IMmotion151 (ITT)[2]	11.2	18
Axitinib + avelumab	JAVELIN Renal 101 (ITT)[3]	13.8	12
Axitinib + pembrolizumab	KEYNOTE-426 (ITT)[4]	15.1	pending
Pembrolizumab monotherapy	KEYNOTE-427[5]	8.7	28.2
TKIs		9-12	20

1. Motzer. NEJM. 2018;378:1277. 2. Motzer. Genitourinary Cancers Symposium 2018. Abstr 578. 3. Motzer. ESMO 2018. Abstract LBA6.
4. Powels. Genitourinary Cancers Symposium 2019. Abstr 543. 5. McDermott. ASCO 2018. Abstr 4500.


Sunitinib
Pazopanib
1st Line
Progression
Nivolumab
Cabozantinib
Lenvatinib + everolimus
2nd Line
Progression
Everolimus
Axitinib
3rd Line
Longer progression free survival (and overall survival)

Conclusions

- The goal of a patient with newly metastatic RCC is cure; therefore, regimens with the highest chance of cure/durable response, balanced against acceptable toxicity/time off of treatment, should be individualized
- Immunotherapy-based regimens offer the best chance of achieving patient goals
- VEGF inhibitors have immunomodulatory effects with a potential to enhance the anti tumor activity of ICI

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Table of Cor
Discu

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	**Preferred regimens**	**Other recommended regimens**	**Useful under certain circumstances**
Favorable[a]	• Axitinib + pembrolizumab • Pazopanib • Sunitinib	• Ipilimumab + nivolumab • Cabozantinib (category 2B) • Axitinib + avelumab	• Active surveillance[b] • Axitinib (category 2B) • High-dose IL-2[c]
Poor/ intermediate[a]	• Ipilimumab + nivolumab (category 1) • Axitinib + pembrolizumab (category 1) • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab	• Axitinib (category 2B) • High-dose IL-2[c] • Temsirolimus[d]

2nd line

?

2nd line therapies

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NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

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SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY

Preferred regimens	Other recommended regimens	Useful under certain circumstances
• Cabozantinib (category 1) • Nivolumab (category 1) • Ipilimumab + nivolumab	• Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab (category 3)	• Bevacizumab or biosimilar[e] (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients[c] (category 2B) • Temsirolimus[d] (category 2B)

[a] See Risk Models to Direct Treatment (IMDC criteria) (KID-D).
[b] Rini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. Lancet Oncol 2016;17:1317-1324.
[c] Patients with excellent performance status and normal organ function.

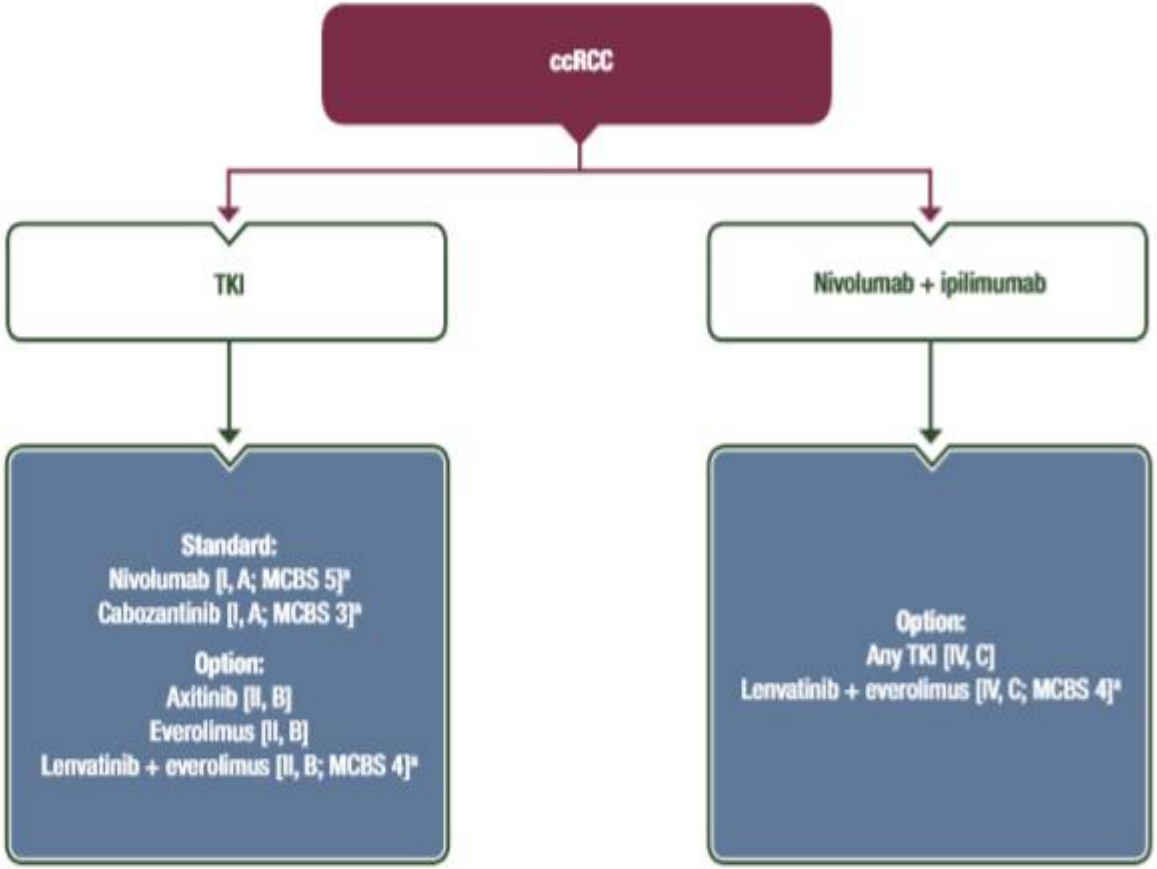


Figure 2. Second-line treatment of ccRCC.

[a]ESMO-MCBS scores for new therapies/indications approved by the EMA since 1 January 2016. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.

ccRCC, clear cell renal cell carcinoma; EMA, European Medicines Agency; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; MCBS, Magnitude of Clinical Benefit Scale; TKI, tyrosine kinase inhibitor.

Therapies after first line

- Cabozantinib, oral TKI
- METEOR III trial showed that cabozantinib has an improved DFS as compared with everolimus as 2.nd line therapy (7.4 mo V 3.8 mo)
- OS was found superior at cabo arm (21.4 mo V16.5 mo)
- Subgroup analysis showed that bone metastatic patients has better DFS rates

Therapies after first line

- AXIS; previously failed from TKI or targeted therapy
  - Axitinib has compared with sorafenib
  - Axitinib has PFS advantage against sorafenib
  - 6.7 mo V 4.7 mo for PFS
  - Well tolerated drug

Therapies after first line

- Lenvatinib+everolimus was compared with everolimus or lenvatinib alone in phase II, randomized multicentered trial
- Median DFS was found superior at combination arm (14.6 mo V 5.5 mo)
- Lenvatinib alone arm was found superior to everolimus alone arm at DFS

Conclusion

- We don’t know the exact drug after ICI or IO now but we will see after new studies for second line or subsequent therapies
- We still have nivo, cabo, everol+lenvatinib, or other TKIs

Cytoreductive nephrectomy

What about cytoreductive nephrectomy?

- Cytoreductive nephrectomy

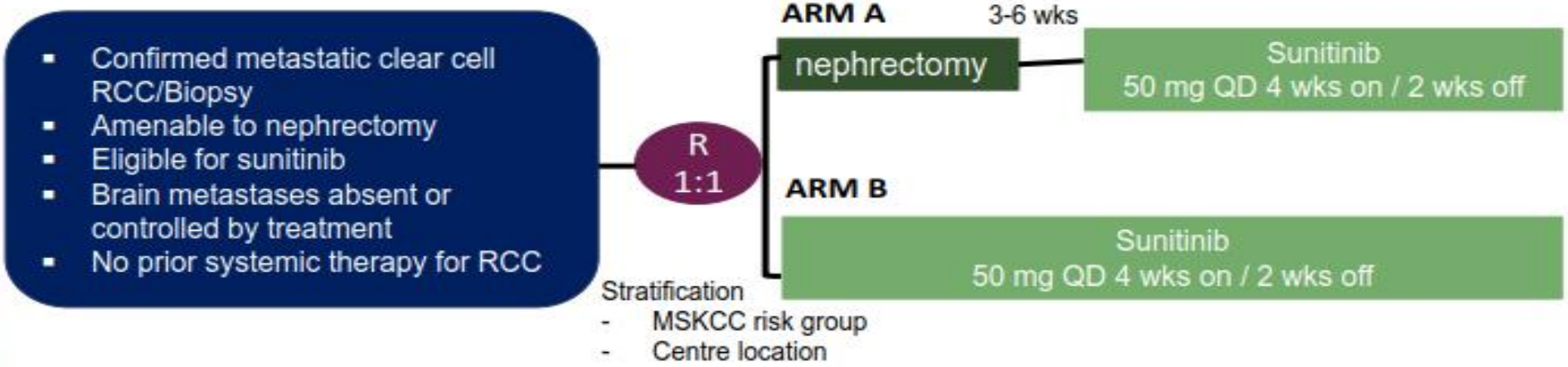
- CARMENA trial

- Treatments during CARMENA

SUNITINIB ALONE OR AFTER NEPHRECTOMY in mRCC

CARMENA: PROSPECTIVE, MULTICENTRE, OPEN-LABEL, RANDOMISED, PHASE III NON-INFERIORITY STUDY

Study design and conduct

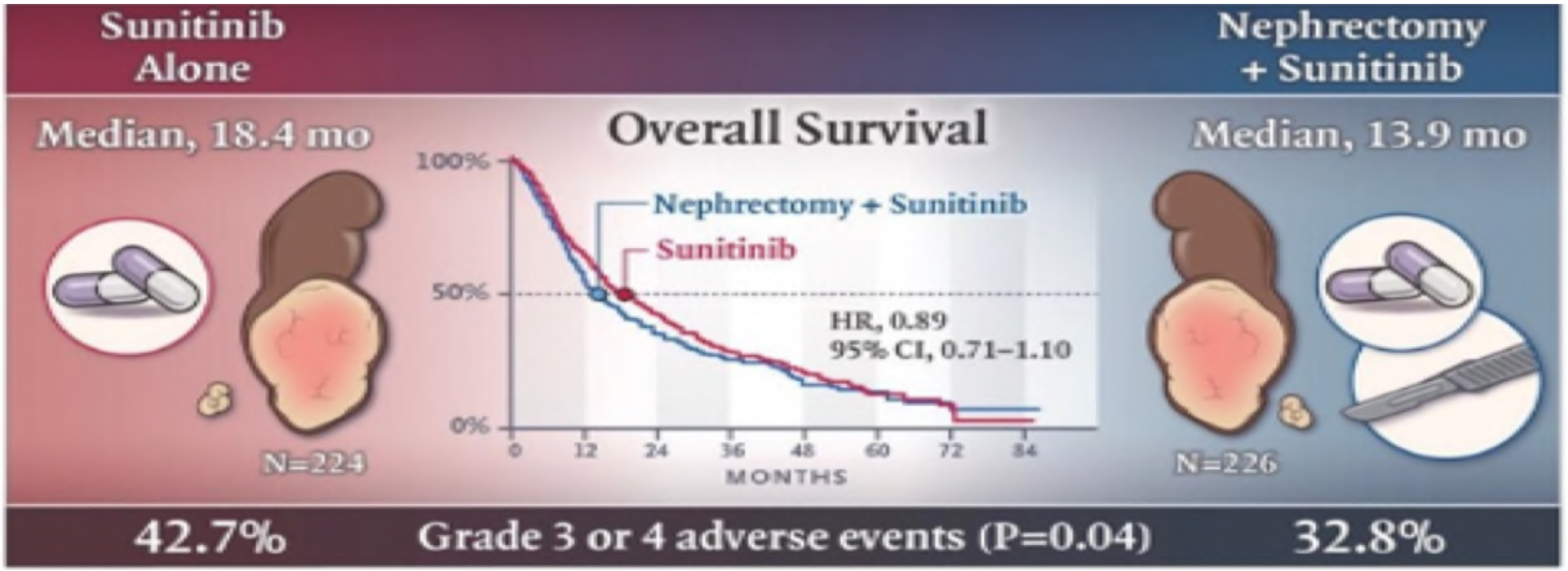


Primary endpoint:
Overall Survival

Primary endpoint:
Progression-free survival, objective response rate, clinical benefit, safety

MSKCC: Memorial Sloan Kettering Center; QD: once daily; R: randomisation; RCC: renal cell carcinoma

Méjean A, *et al.* N Engl J Med. 2018; 379: 417- 427.



The NEW ENGLAND JOURNAL of MEDICINE

Méjean et al. 2018

Median OS, months (95% CI)	Arm A: Nephrectomy + Sunitinib (n=226)	Arm B: Sunitinib Alone (n=224)	HR (95% CI)
Overall	13.9 (11.8-18.3)	18.4 (14.7-23.0)	0.89 (0.71-1.10)
MSKCC intermediate risk	19.0 (12.0-28.0)	23.4 (17.0-32.0)	0.92 (0.6-1.24)
MSKCC poor risk	10.2 (9.0-14.0)	13.3 (9.0-17.0)	0.86 (0.62-1.17)

Non-inferiority study ≤ 1.20

SUMMARY

- Using either the IMDC or MSKCC criteria, CN is not the standart of care.

- In the poor risk group, patients receiving sunitinib alone had better overall survival compared with patients receiving CN.

- The number of metastatic sites did not correlate with overall survival outcomes.

- Patients with delayed nephrectomy had longer OS .


Thank you for your attention!