Cancer du rein métastatique
Traitement de 1ère ligne

Pr Jean-Alexandre Long

CHU Grenoble

Cette réunion est organisée par Bristol-Myers Squibb SARL

Liens d’intérêt

- BMS
- Astellas
- TAKEDA
- IPSEN

Le contenu et/ou les opinions exprimées lors de cette présentation, notamment celui ou celle(s) relatifs à la stratégie thérapeutique ont été réalisés en toute indépendance

Evaluation Pronostique du CCR métastatique

	Original model[7] (n=564)*		Validation (n=849)	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
KPS <80%	2·51 (1·92–3·29)	<0·0001	2·08 (1·71–2·55)	<0·0001
<1 year from diagnosis to treatment	1·42 (1·09–1·84)	0·0098	1·27 (1·05–1·53)	0·0122
Haemoglobin concentration <lower limit of normal	1·72 (1·31–2·26)	0·0001	1·69 (1·38–2·06)	<0·0001
Calcium concentration >upper limit of normal	1·81 (1·29–2·53)	0·0006	1·45 (1·10–1·92)	0·0087
Neutrophil count >upper limit of normal	2·42 (1·72–3·39)	<0·0001	1·64 (1·31–2·05)	<0·0001
Platelet count >upper limit of normal	1·49 (1·09–2·03)	0·0121	1·60 (1·28–2·01)	<0·0001

Table 5. Median OS estimates in first- and second-line RCC according to IMDC risk groups

Number of risk factors	Risk category	Median OS (months)	
		First line [24]	Second line [23]
0	Favourable	43.2	35.3
1–2	Intermediate	22.5	16.6
3–6	Unfavourable	7.8	5.4

IMDC, International Metastatic RCC Database Consortium; OS, overall survival; RCC, renal cell carcinoma.

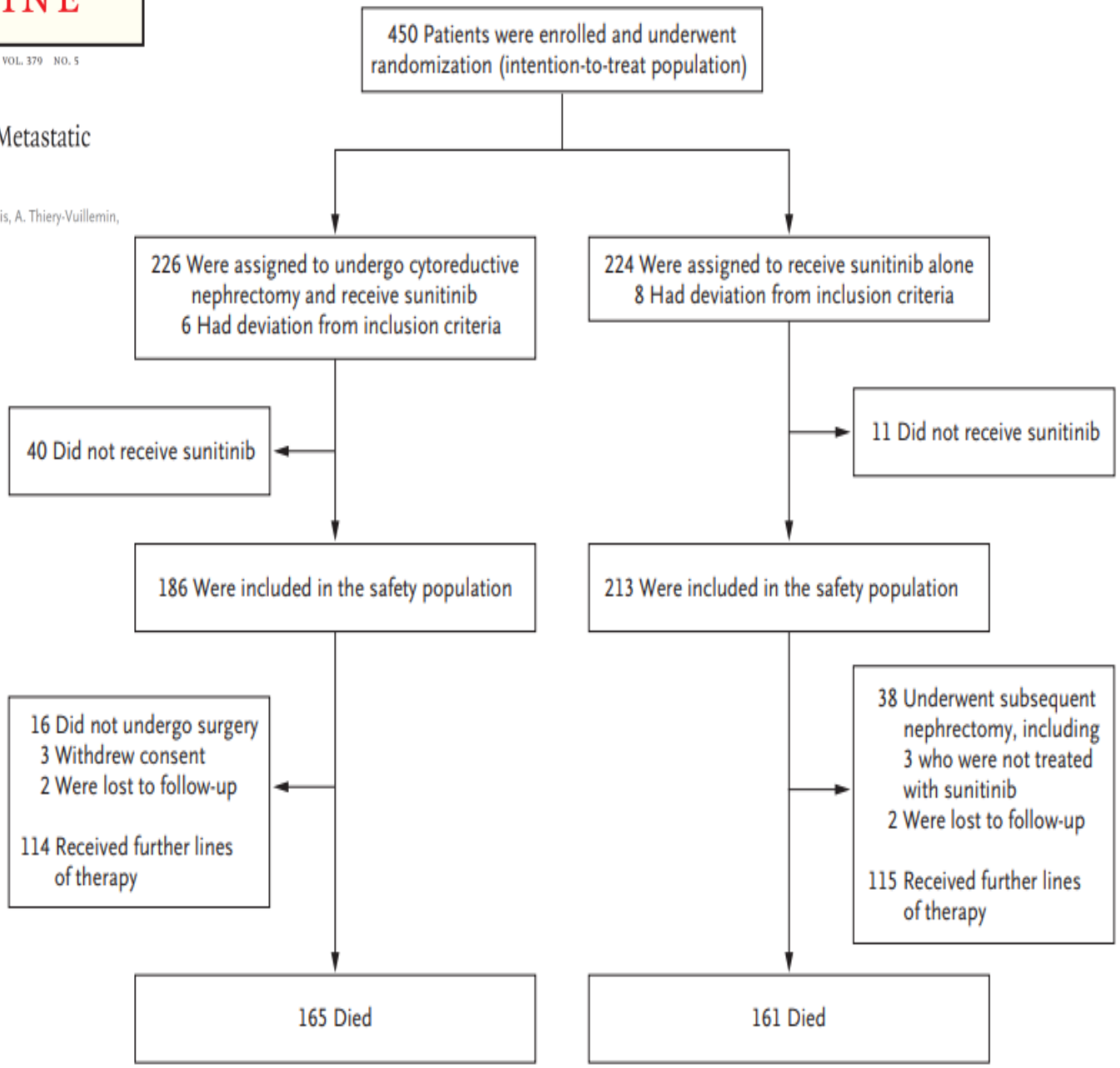
Bon=0 ; Intermédiaire=1 à 2
Défavorable≥3

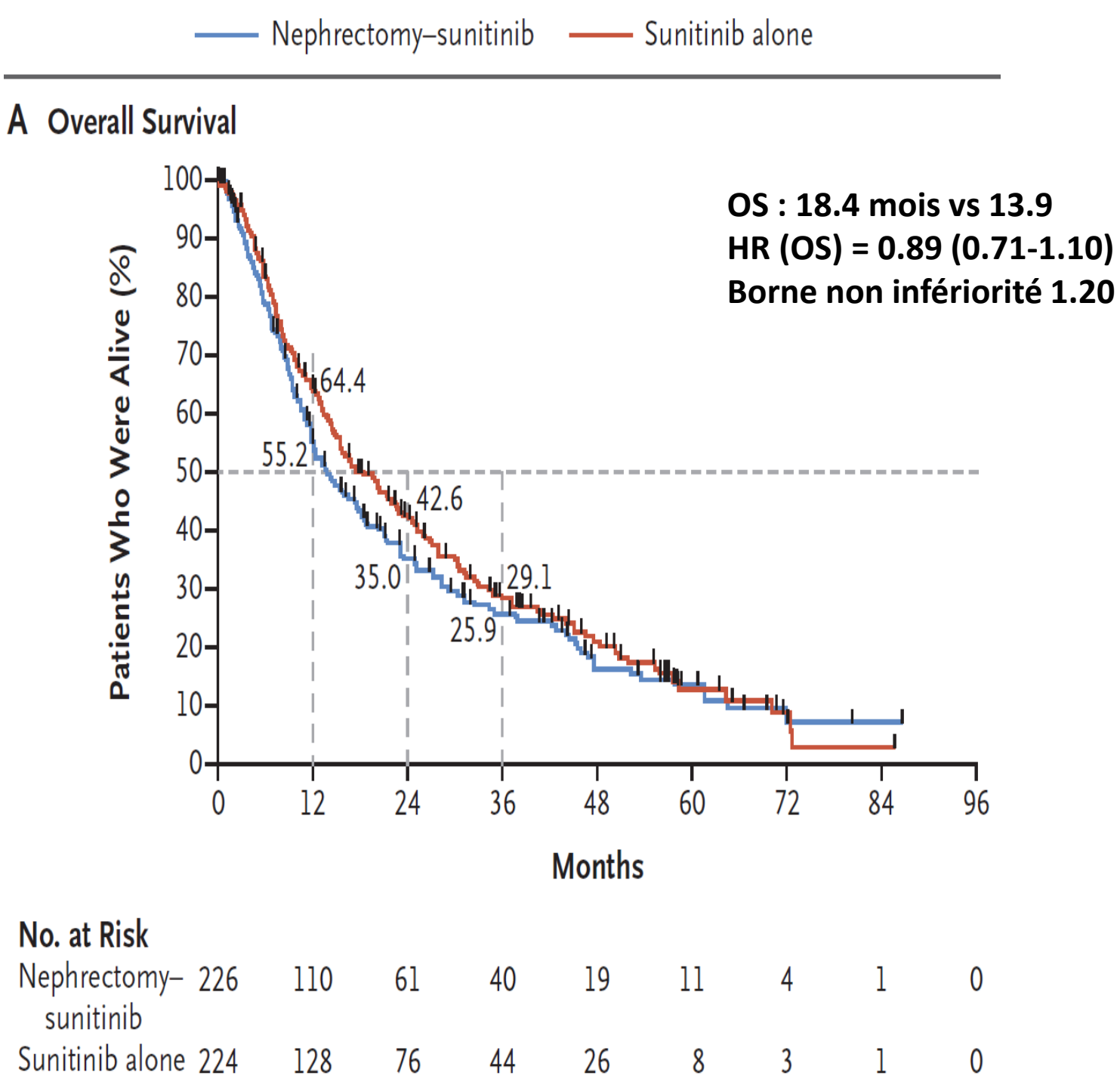
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 2, 2018 VOL. 379 NO. 5

Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma

A. Méjean, A. Ravaud, S. Thezenas, S. Colas, J.-B. Beauval, K. Bensalah, L. Geoffrois, A. Thiery-Vuillemin,





OS : 18.4 mois vs 13.9
HR (OS) = 0.89 (0.71-1.10)
Borne non infériorité 1.20

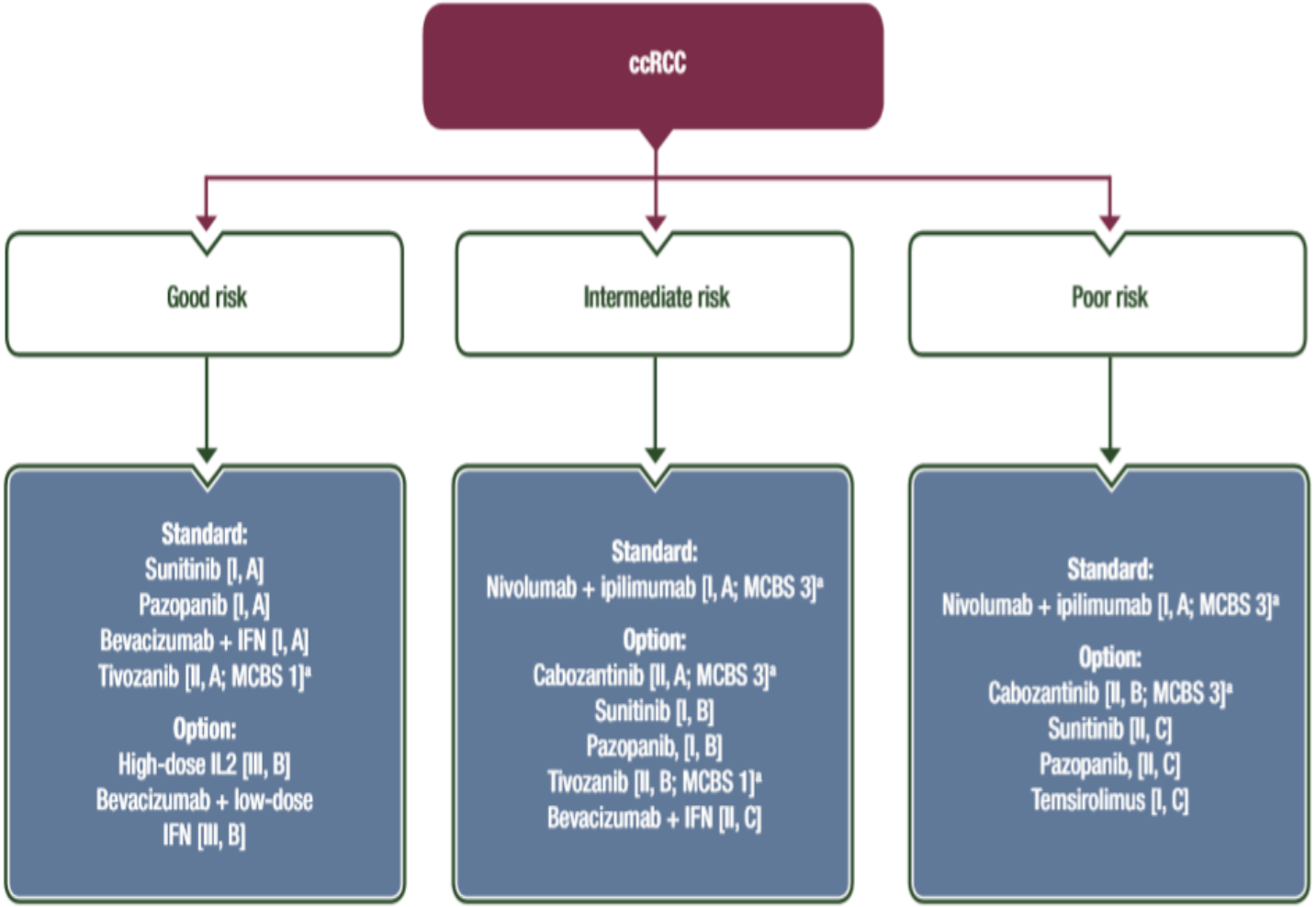
Place de la Néphrectomie

Patients risque défavorable = pas de néphrectomie (encore que..)

Patients risque intermédiaire = à discuter

Patients risque favorable M+ d'emblée = n'existe pas…

ESMO Guidelines



Sunitinib

- **Réponse objective**
- **Survie sans progression**
- **Effets indésirables**

The NEW ENGLAND JOURNAL of MEDICINE

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

Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

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

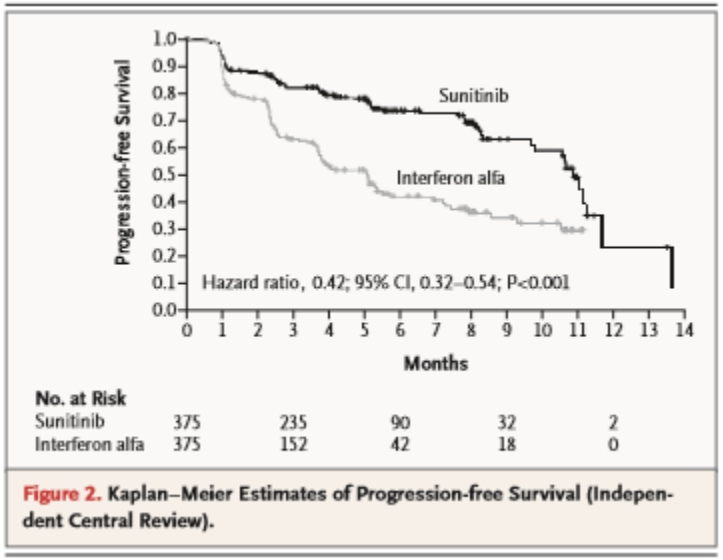
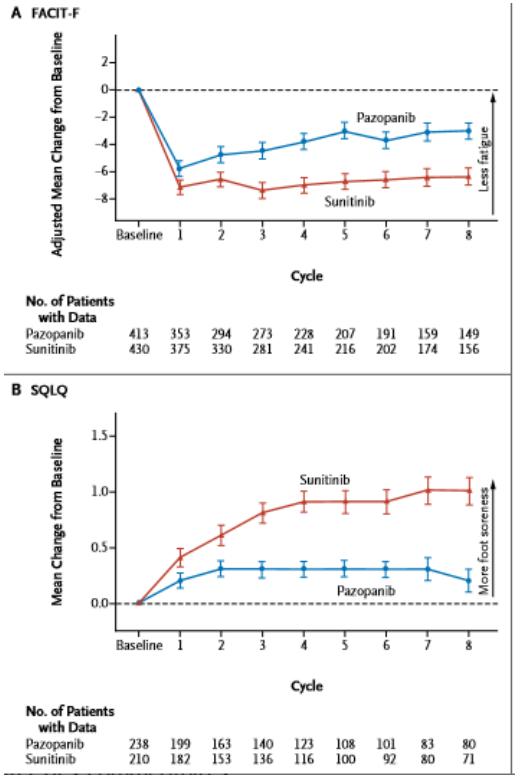


Figure 2. Kaplan–Meier Estimates of Progression-free Survival (Independent Central Review).

Pazopanib

- **Etude non infériorité / Sunitinib**
- **Meilleur taux de réponse**
- **Tolérance**



ORIGINAL ARTICLE

Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma

Robert J. Motzer, M.D., Thomas E. Hutson, D.O., David Cella, Ph.D., James Reeves, M.D., Robert Hawkins, M.B., B.S., Ph.D., Jun Guo, Ph.D., Paul Nathan, M.B., B.S., Ph.D., Michael Staehler, M.D., Paul de Souza, M.B., B.S., Ph.D., Jaime R. Merchan, M.D., Ekaterini Boleti, M.D., Ph.D., Kate Fife, M.D., Jie Jin, M.D., Robert Jones, Ph.D., Hirotsugu Uemura, M.D., Ph.D., Ugo De Giorgi, M.D., Ulrika Harmenberg, M.D., Ph.D., Jinwan Wang, M.D., Cora N. Sternberg, M.D., Keith Deen, M.S., Lauren McCann, Ph.D., Michelle D. Hackshaw, Ph.D., Rocco Crescenzo, D.O., Lini N. Pandite, M.D., and Toni K. Choueiri, M.D.

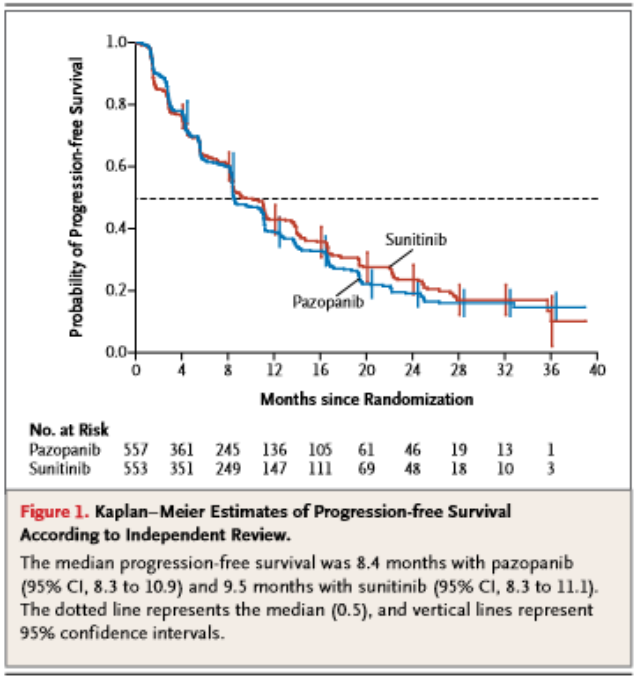


Figure 1. Kaplan–Meier Estimates of Progression-free Survival According to Independent Review.

The median progression-free survival was 8.4 months with pazopanib (95% CI, 8.3 to 10.9) and 9.5 months with sunitinib (95% CI, 8.3 to 11.1). The dotted line represents the median (0.5), and vertical lines represent 95% confidence intervals.

Nivolumab + Ipilimumab CheckMate 214

Phase 3, randomized, open-label trial of nivolumab combined with ipilimumab vs sunitinib monotherapy in treatment-naïve patients with advanced or metastatic clear cell RCC[1]

N=139

Key Inclusion Criteria[a]

- Advanced/metastatic clear cell RCC
- No prior systemic therapy for RCC
- Prior adjuvant/neoadjuvant therapy allowed if the agent did not target the VEGF pathway, and recurrence occurred ≥6 months after last dose
- KPS ≥70%
- Available FFPE archival or recent tumor tissue sample
- No prior treatment with VEGF pathway agents or agents targeting T-cell co-stimulation or checkpoint pathways
- No current or history of CNS metastases

R 1:1

Nivolumab
3 mg/kg IV q3w for 4 doses, then q2w

Patients receiving NIVO monotherapy could switch to NIVO 240 mg flat dosing

Ipilimumab
1 mg/kg IV q3w for 4 doses

Sunitinib
50 mg PO qd for 4 weeks (6-week cycles)

Crossover from SUN to NIVO+IPI was permitted

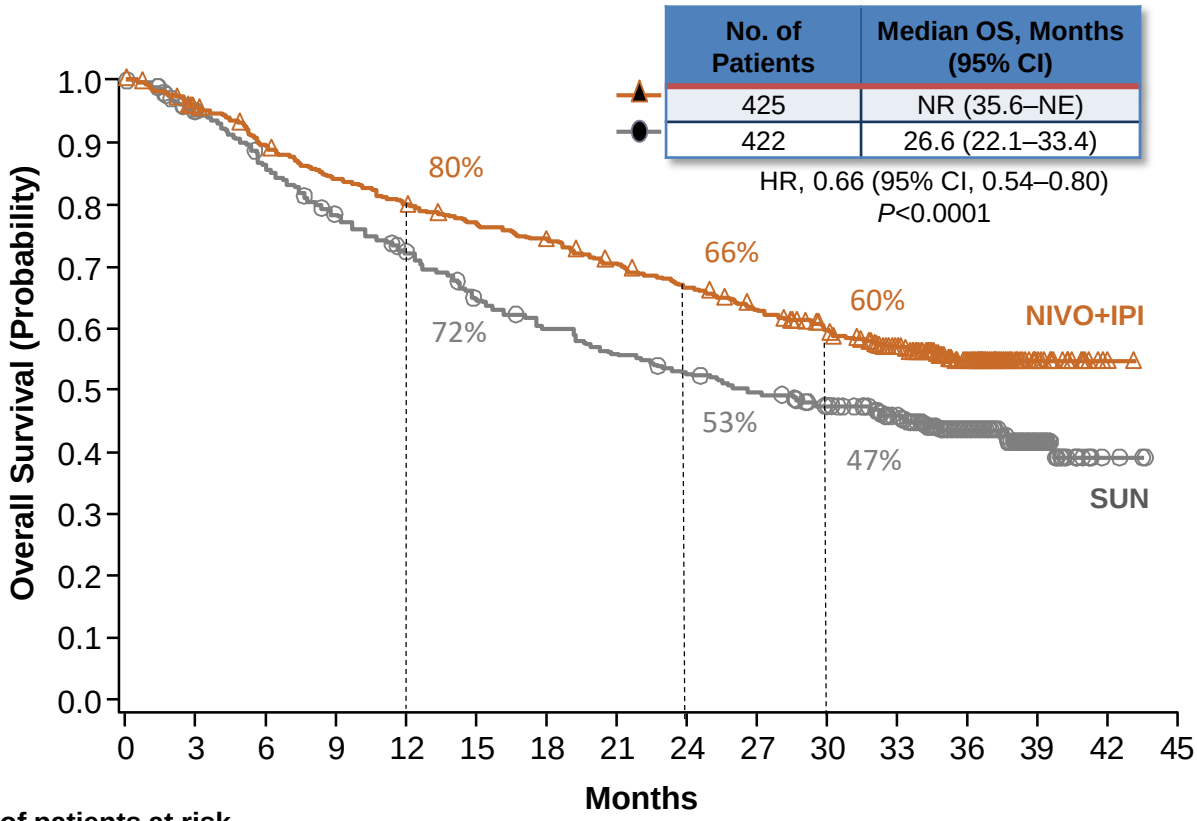
Until progression,[b] unacceptable toxicity, withdrawal of consent, or end of trial (up to 5 years)[c]

Primary Outcome Measures: PFS, OS, ORR in intermediate/poor-risk patients[2,3]

Key Secondary Outcome Measures: PFS, OS, and ORR in any-risk patients, incidence of AEs[2,3]

Select Exploratory Outcome Measures: PFS and OS in favorable-risk patients, HRQoL[2,3]

OS: IMDC Intermediate/Poor-Risk



No. of patients at risk

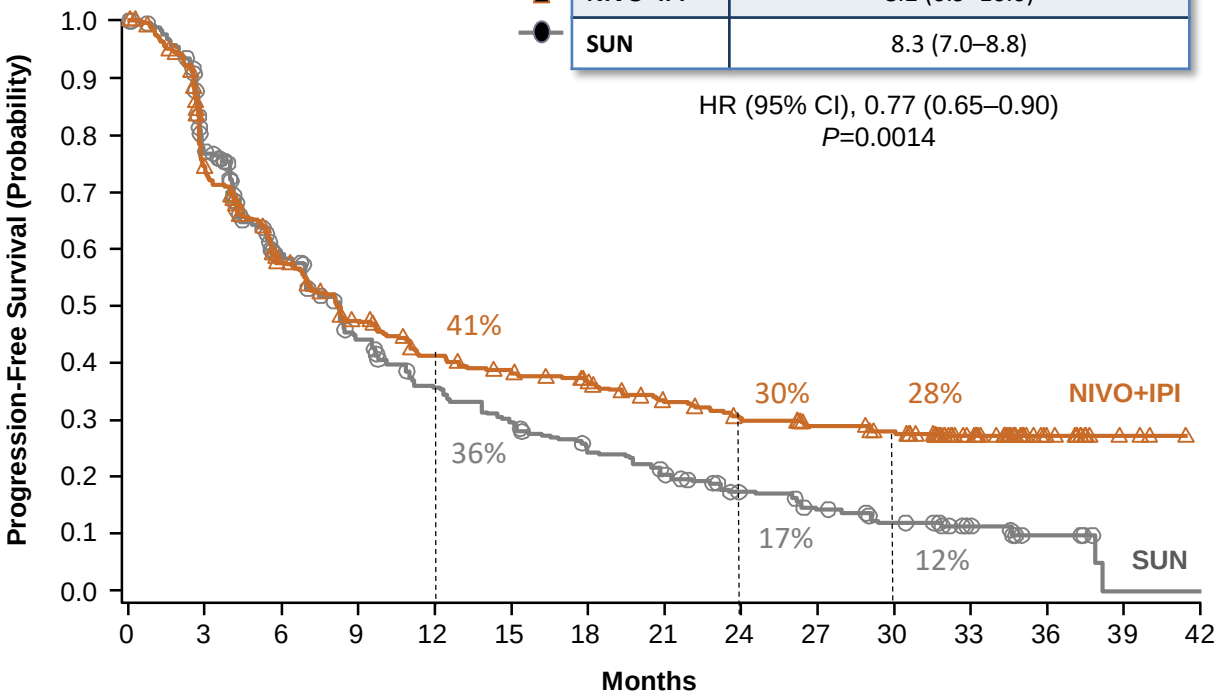
NIVO+IPI	425	399	372	348	332	317	306	287	270	253	233	183	90	34	2	0
SUN	422	388	353	318	290	257	236	220	207	194	179	144	75	29	3	0

Based on data cutoff of August 6, 2018.
CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IPI, ipilimumab; NE, not estimable; NIVO, nivolumab; NR, not reached; OS, overall survival; SUN, sunitinib.

PFS: IMDC Intermediate/Poor Risk

Median PFS,[a] 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

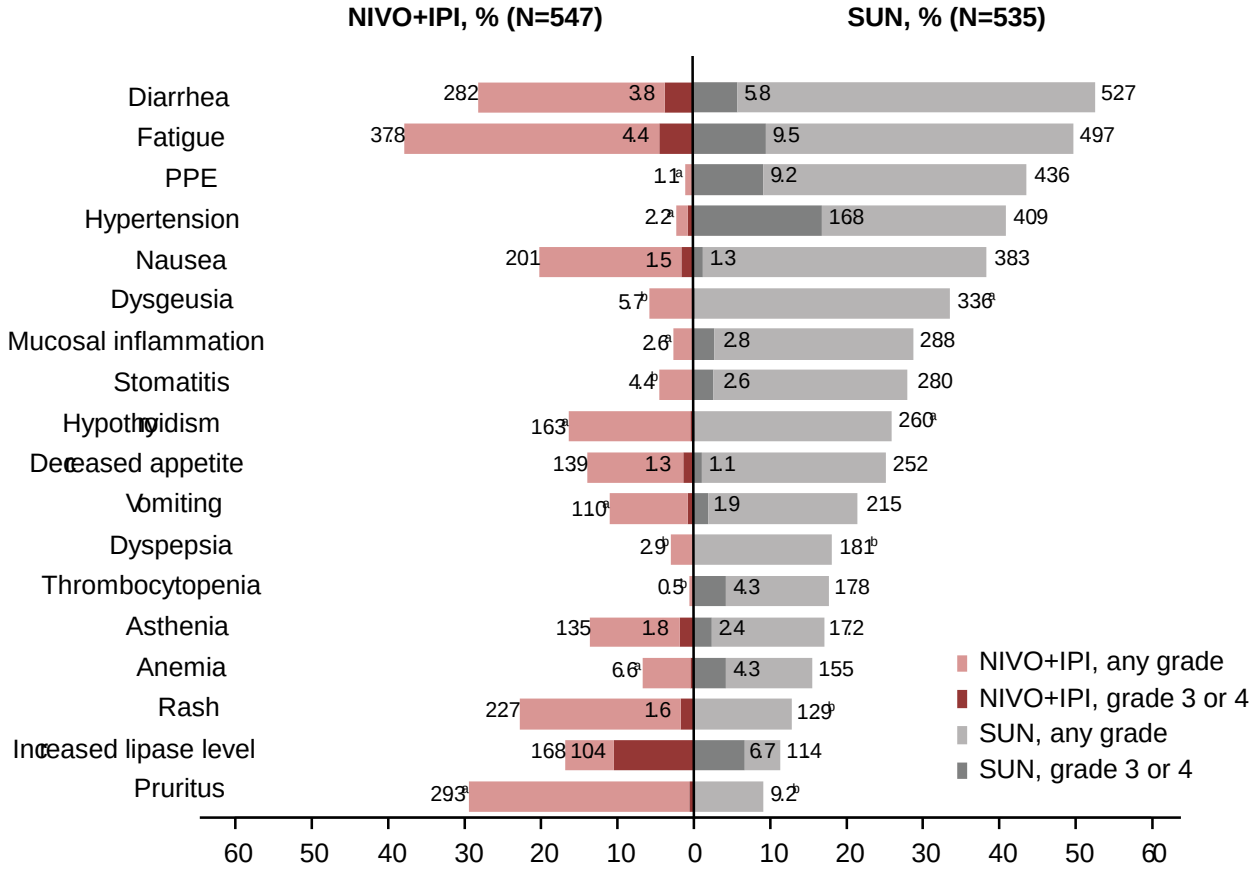


No. of patients at risk

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

Based on data cutoff of August 6, 2018.
[a]Per RECIST v1.1.
CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IPI, ipilimumab; NIVO, nivolumab;
PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SUN, sunitinib.
Adapted with permission from Tannir NM et al. Oral presentation at ASCO GU 2019.

Any-Grade Treatment-Related AEs Occurring in >15% of Patients in Either Arm: All Treated Patients



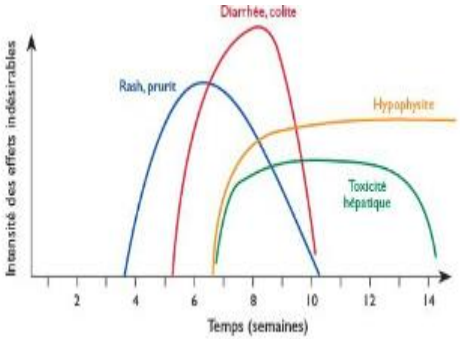
- **Any-grade treatment-related AEs occurred in 513/547 (94%) NIVO+IPI–treated patients and in 521/535 (97%) SUN-treated patients**

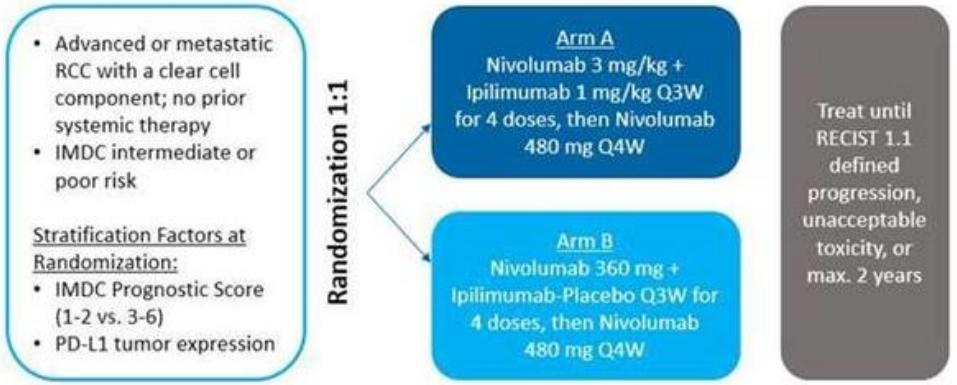
Based on data cutoff of August 6, 2018.
[a]<1% reported grade 3–4 treatment-related AE. [b]No patients reported a grade 3–4 treatment-related AE.
AE, adverse event; PPE, palmoplantar erythrodysesthesia.
Included with permission from Tannir NM et al. Poster presentation at ASCO GU 2019.

Toxicité de l'association anti PD-1 - anti CTLA4

- **Anti-CTLA4:**
  - 17 à54% de diarrhées
  - 8 à 22% d'entérocolites

- **La toxicité de cette combinaison est plus importante que les deux monothérapies**
  - 54% de toxicité de grade 3 ou 4 avec la combinaison
  - 24% avec l'ipilimumab seul



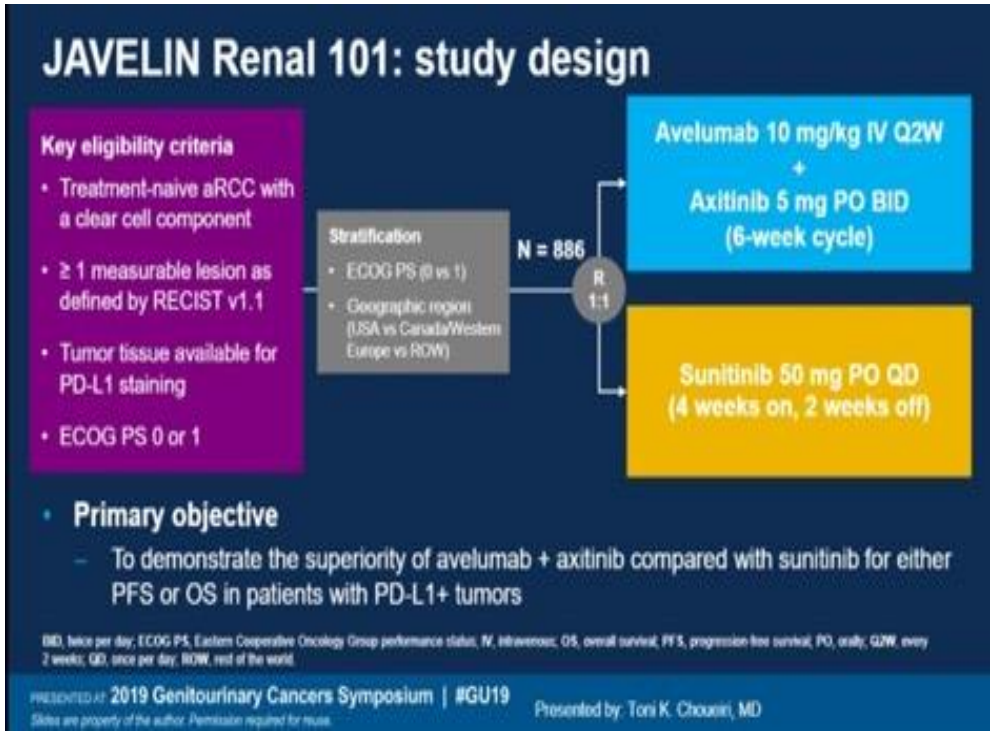


JAVELIN

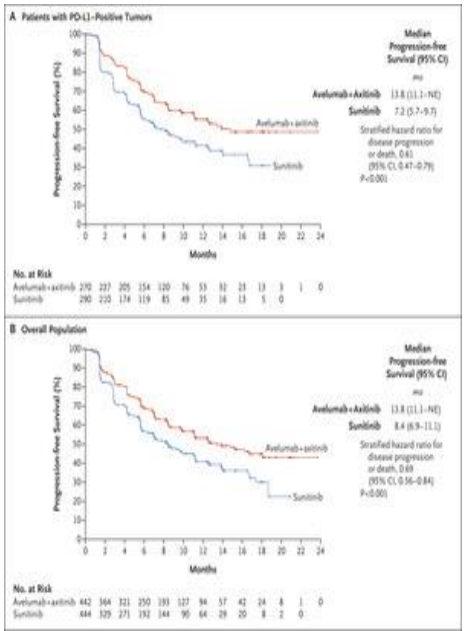
ORIGINAL ARTICLE FREE PREVIEW

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.



March 21, 2019
N Engl J Med 2019; 380:1103-1115
DOI: 10.1056/NEJMoa1816047

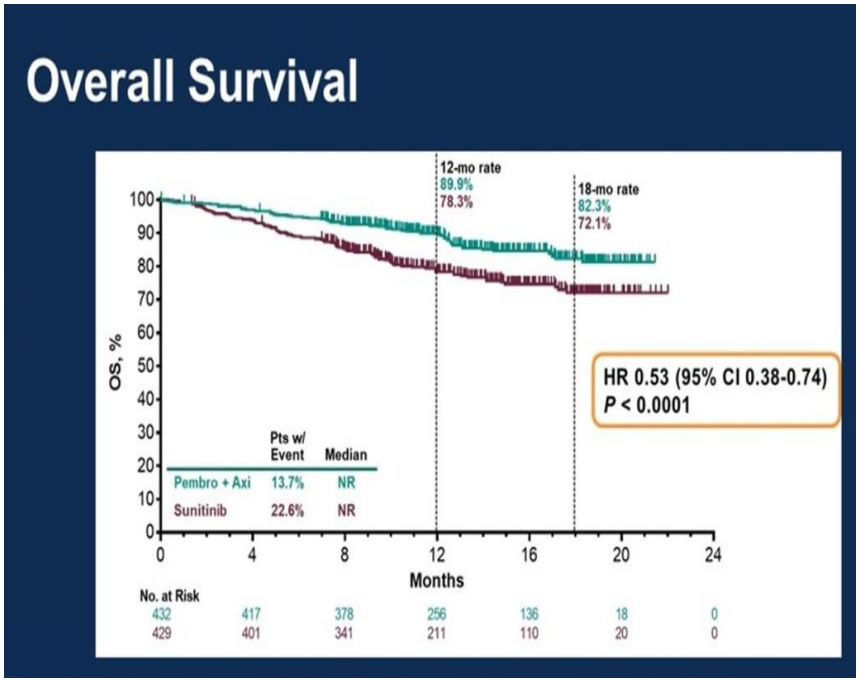


KEYNOTE 426

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*



Cabozantinib

VOLUME 35 · NUMBER 6 · FEBRUARY 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

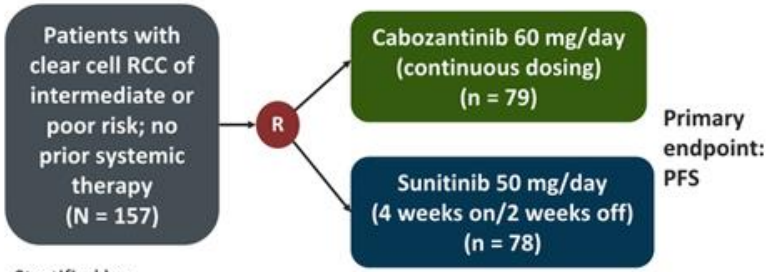
ORIGINAL REPORT

Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial

Toni K. Choueiri, Susan Halabi, Ben L. Sanford, Olwen Hahn, M. Dror Michaelson, Meghara K. Walsh, Darren R. Feldman, Thomas Olencki, Joel Picus, Eric J. Small, Shaker Dakhil, Daniel J. George, and Michael J. Morris

Cabozantinib vs Sunitinib in Untreated Clear Cell RCC: CABOSUN Study

- Multicenter, randomized, phase 2 study

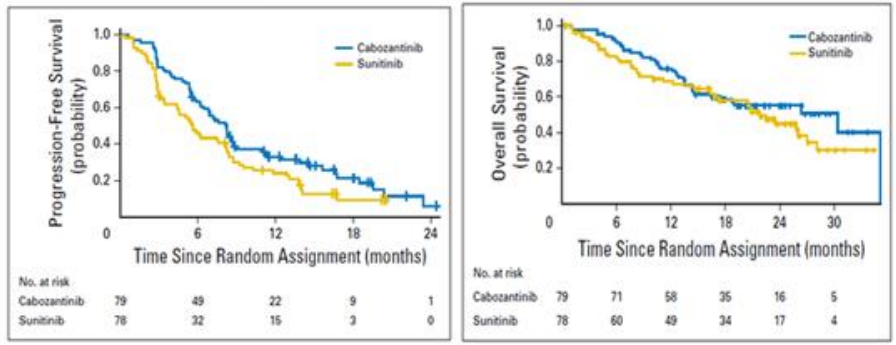


Stratified by:
- IMDC risk group (intermediate vs poor)
- Bone metastasis (yes/no)

Choueiri TK, et al. *J Clin Oncol*. 2017;35:591-597.

Medscape EDUCATION

CABOSUN Study *Efficacy Results*



- Cabozantinib improved PFS vs sunitinib (8.2 months vs 5.6 months; HR, 0.66; $P = .012$)
- 34% reduction in median rate of progression
- ORR: 46% vs 18% for cabozantinib vs sunitinib, respectively

Reprinted from The Lancet, Vol. 17, Choueiri TK, Esudier B, Pweles T, et al, Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial, 917-927, Copyright 2016, with permission from Elsevier.

Medscape EDUCATION

Conclusion: 1ère ligne métastatique

- **Situation française actuelle**
  - Sunitinib
  - Pazopanib
- **Les données de la littérature**
  - Nivolumab – Ipilumab (risque intermédiaire et élevé)
  - Sunitinib / Pazopanib (risque faible)
- **Place de l'association TKI-immunothérapie**