Controversias

Estrategia óptima de secuenciación en cáncer renal.

carmenbeato10
cbeatoz@hotmail.com

AGENDA

- INTRODUCCIÓN
- CLASIFICACIÓN PRONÓSTICA
- GUÍAS CLÍNICAS: 1° LINEA CC
- GUÍAS CLÍNICAS: SUCESIVAS
- CONCLUSIONES


And all this in
only 15 minutes

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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.*

ABSTRACT

BACKGROUND

Since sunitinib malate has shown activity in two uncontrolled studies in patients From the Memorial Sloan-Kettering Can-

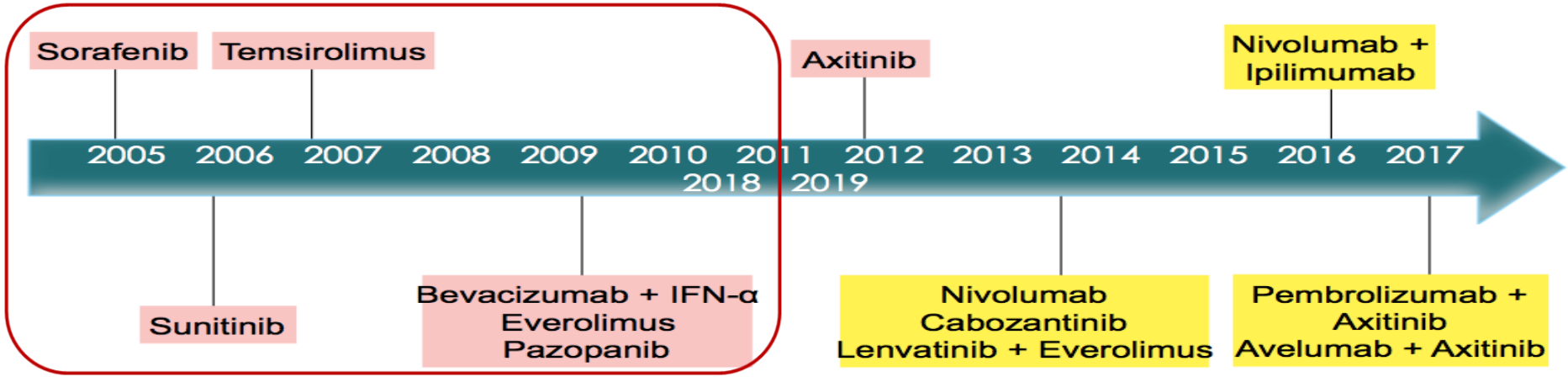
The NEW ENGLAND JOURNAL of MEDICINE

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.

ABSTRACT



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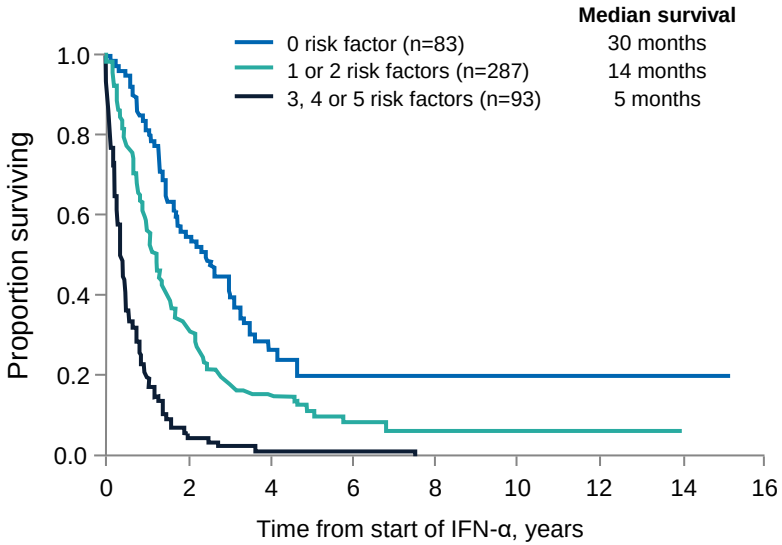
CLASIFICACIONES PRONÓSTICAS

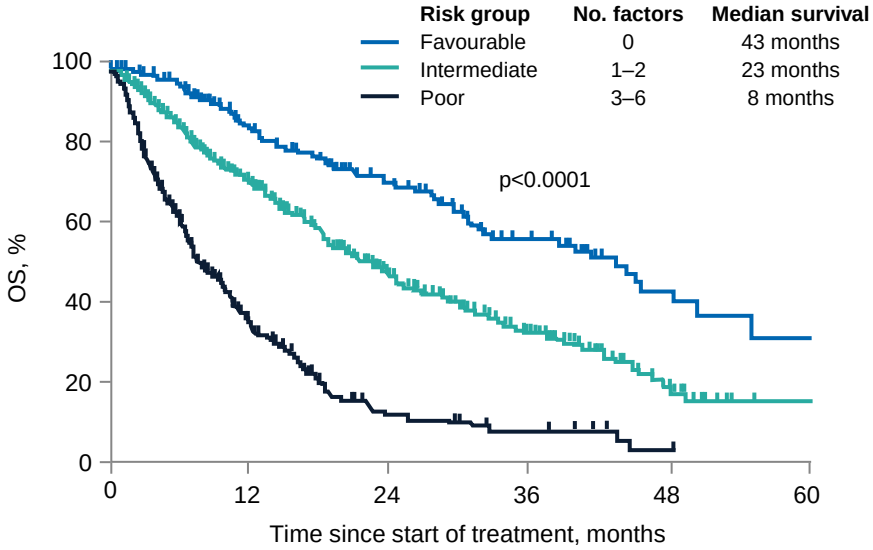
MSKCC: Before targeted therapies (IFN-α)



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

Motzer RJ, et al. J Clin Oncol 2002;20:289–96

IMDC: VEGF-targeted therapies



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

Heng DY, et al. Lancet Oncol 2013;14:141–48

AGENDA

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- GUÍAS CLÍNICAS: SUCESIVAS
- CONCLUSIONES

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

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

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• Cabozantinib (category 1) • Nivolumab[b] (category 1) • Ipilimumab + nivolumab[b]	• Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab[b] • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab[b] (category 3)	• Bevacizumab[f] (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B)

JULIO 2020

[a] See Risk Models to Direct Treatment (IMDC criteria or MSKCC Prognostic Model) (KID-D).
[b] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[c] 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.
[d] Patients with excellent performance status and normal organ function.
[e] The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium >10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-2281.
[f] An FDA-approved biosimilar is an appropriate substitution for bevacizumab.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	**Preferred regimens**	**Other recommended regimens**	**Useful in certain circumstances**
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JULIO 2020

Clinical and Translational Oncology (2020) 22:256–269
https://doi.org/10.1007/s12094-019-02285-7

CLINICAL GUIDES IN ONCOLOGY

Check for updates

SEOM clinical guideline for treatment of kidney cancer (2019)

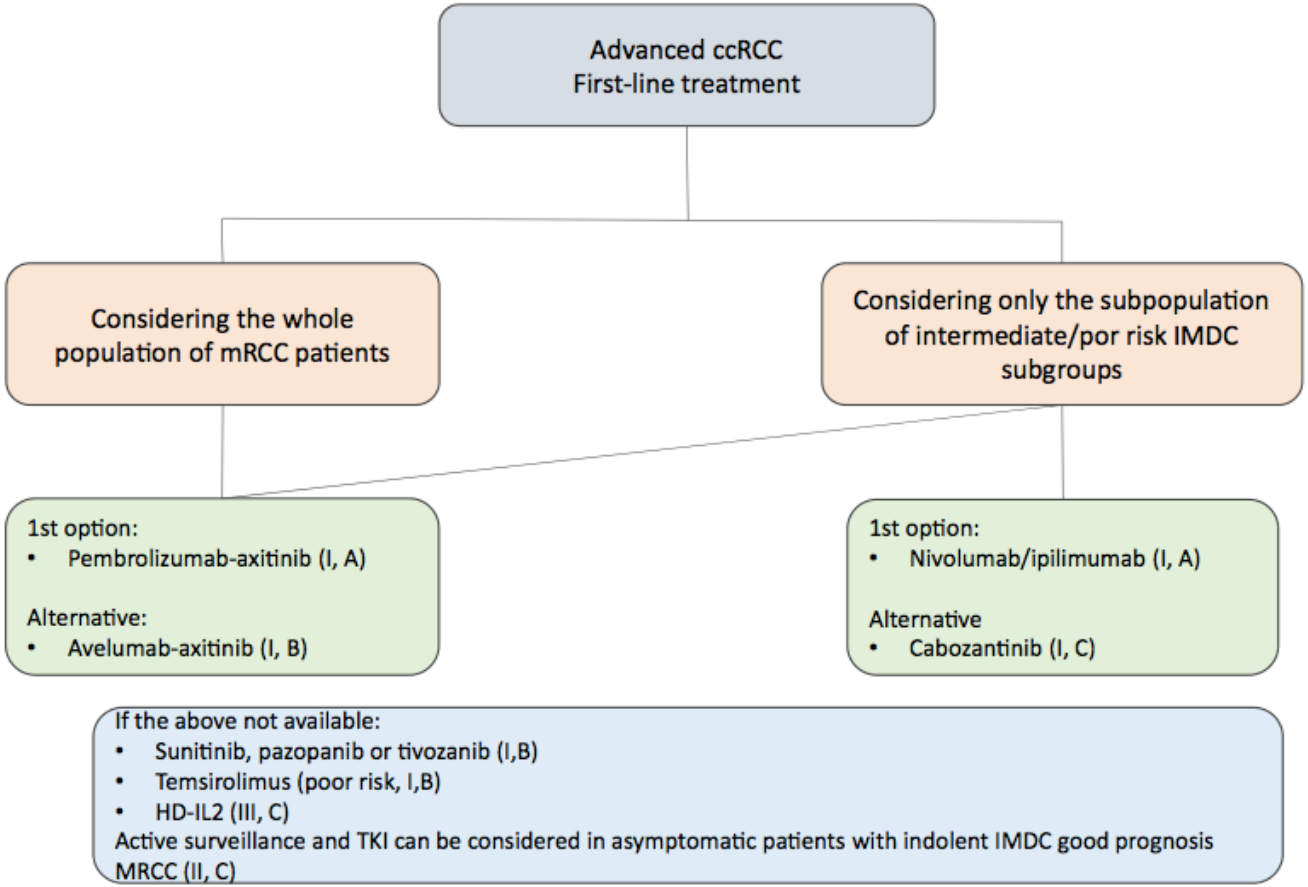
M. Lázaro[1] · B. P. Valderrama[2] · C. Suárez[3] · G. de-Velasco[4] · C. Beato[5] · I. Chirivella[6] · A. González-del-Alba[7] · N. Laínez[8] · M. J. Méndez-Vidal[9] · J. A. Arranz[10]

Received: 26 December 2019 / Accepted: 26 December 2019 / Published online: 28 January 2020

Abstract

- **Cytoreductive nephrectomy** not mandatory in patients with intermediate–poor IMDC/MSKCC risk who require systemic therapy. **Level of evidence: I. Grade of recommendation: A.** CN for limited metastatic burden amenable to **surveillance** or metastasectomy, in patients requiring palliation, and potentially delayed therapy. **Level of evidence: II. Grade of recommendation: B.**

- **Metastasectomy** for selected patients, limited number of metastases, long metachronous FPS. **Level of evidence: II. Grade of recommendation: C.**


Advanced ccRCC
First-line treatment
Considering the whole population of mRCC patients
Considering only the subpopulation of intermediate/por risk IMDC subgroups
1st option:
• Pembrolizumab-axitinib (I, A)
Alternative:
• Avelumab-axitinib (I, B)
1st option:
• Nivolumab/ipilimumab (I, A)
Alternative
• Cabozantinib (I, C)
If the above not available:
• Sunitinib, pazopanib or tivozanib (I,B)
• Temsirolimus (poor risk, I,B)
• HD-IL2 (III, C)
Active surveillance and TKI can be considered in asymptomatic patients with indolent IMDC good prognosis MRCC (II, C)

PRIMERA LÍNEA: Ensayos recientes

- CheckMate 214: Ipilimumab/nivolumab vs sunitinib (OS benefit)
- KEYNOTE-426: Pembrolizumab/axitinib vs sunitinib (OS benefit)

- Others:
  - Avelumab/axitinib vs sunitinib (PFS benefit, FDA approved)
  - Atezolizumab/bevacizumab vs sunitinib (PFS benefit, not approved)
  - Pembrolizumab/lenvatinib vs sunitinib (completed, not yet reported)
  - Nivolumab/cabozantinib vs sunitinib (completed, not yet reported) ------

Ya si, lo vemos luego

Slide credit: clinicaloptions.com

IO + IO

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 5, 2018 VOL. 378 NO. 14

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, E.R. Plimack, P. Barthélémy, C. Porta, S. George, T. Powles, F. Donskov, V. Neiman, C.K. Kollmannsberger, P. Salman, H. Gurney, R. Hawkins, A. Ravaud, M.-O. Grimm, S. Bracarda, C.H. Barrios, Y. Tomita, D. Castellano, B.I. Rini, A.C. Chen, S. Mekan, M.B. McHenry, M. Wind-Rotolo, J. Doan, P. Sharma, H.J. Hammers, and B. Escudier, for the CheckMate 214 Investigators*

Motzer RJ, et al. N Engl J Med 2018;378(14):1277-90

CHECKMATE-214

IO + IO

Treatment-naïve mRCC with a clear-cell component

N = 1070

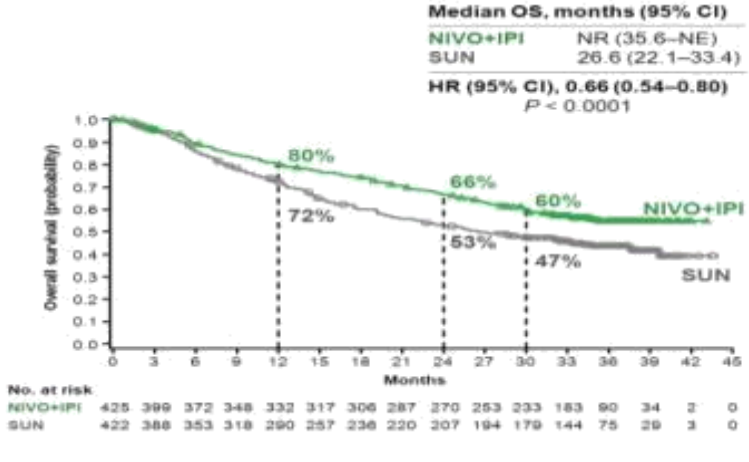
Randomize 1:1

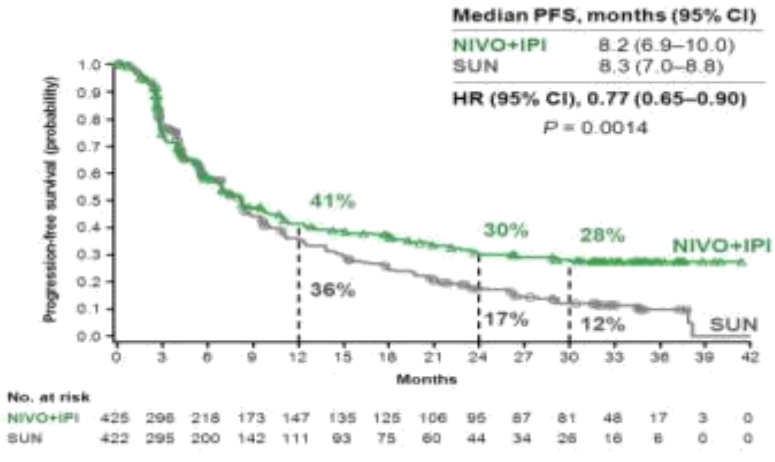
Nivolumab 3 mg/kg plus Ipilimumab 1 mg/kg IV every 3 weeks x 4 doses then Nivolumab 3 mg/kg every 2 weeks

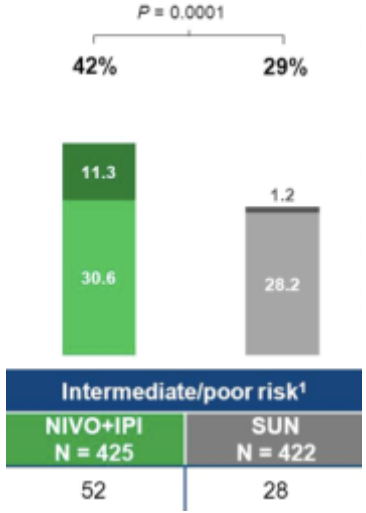
Sunitinib 50 mg orally once daily 4w on/2w off

INTERMEDIATE- AND POOR-RISK PATIENTS

Co-primary endpoint: ORR, PFS and OS in intermediate- and poor-risk patients







Motzer RJ, et al. N Engl J Med 2018;378(14):1277-90
Motzer RJ, et al. Lancet Oncol 2019;20(10):1370-1385

CHECKMATE-214

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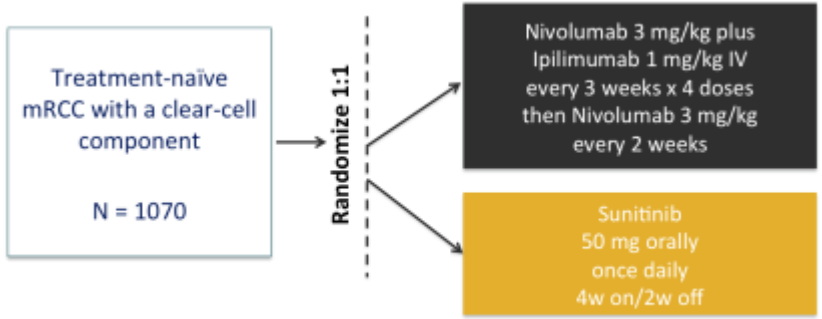
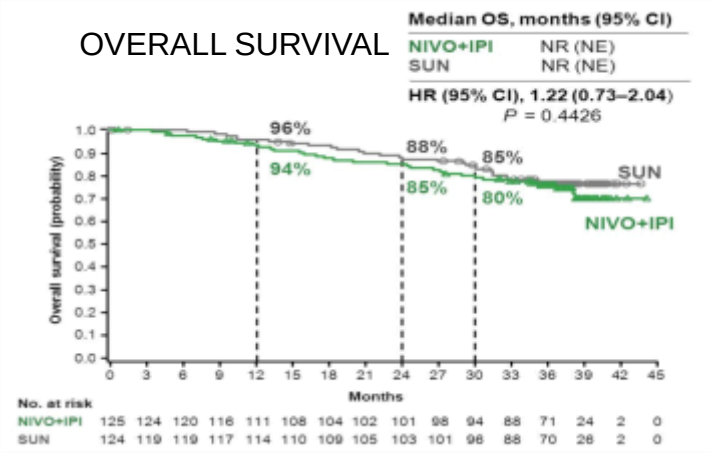
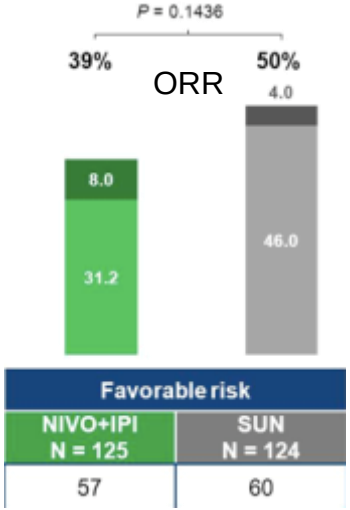
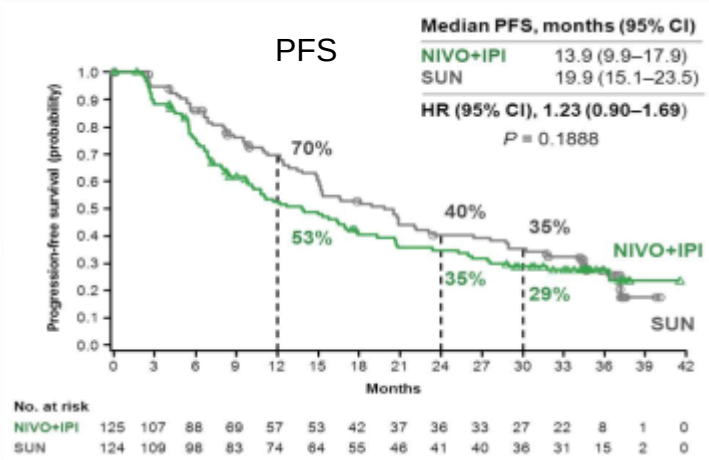


Co-primary endpoint: ORR, PFS and OS in intermediate- and poor-risk patients

GOOD RISK PATIENTS







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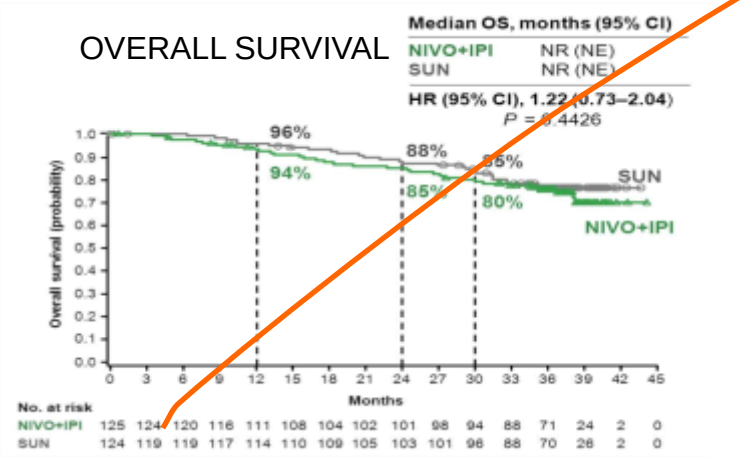
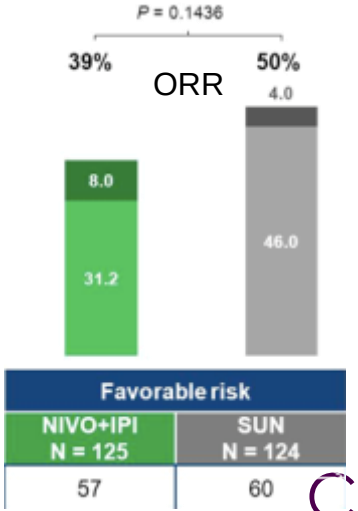
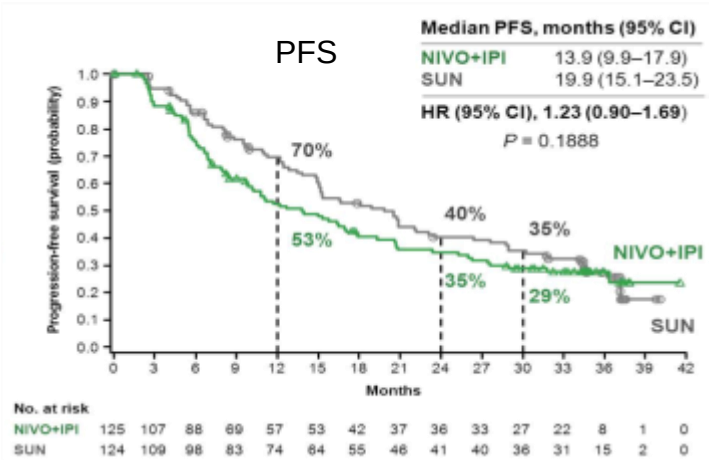
OVERALL SURVIVAL





PFS



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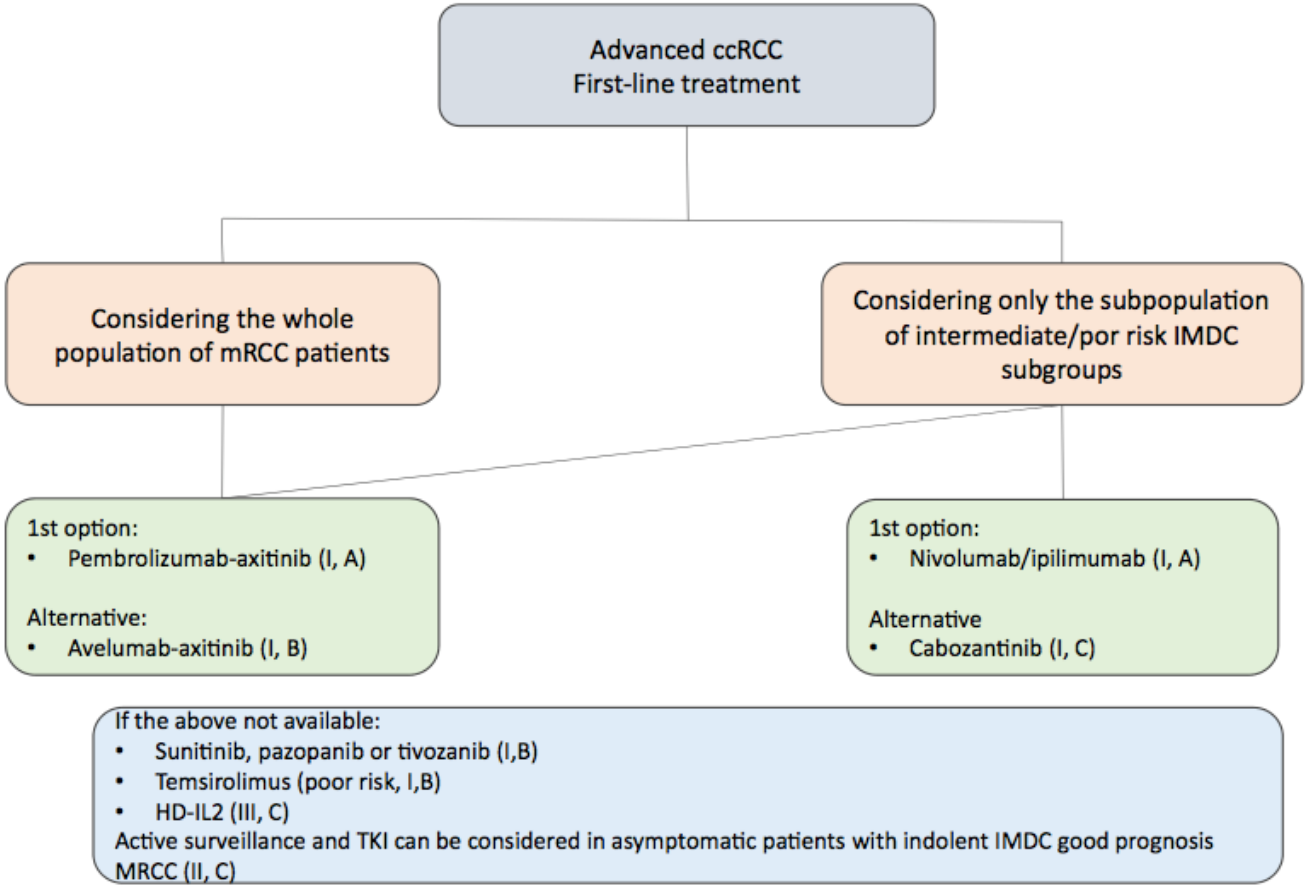
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Considering the whole population of mRCC patients
Considering only the subpopulation of intermediate/por risk IMDC subgroups
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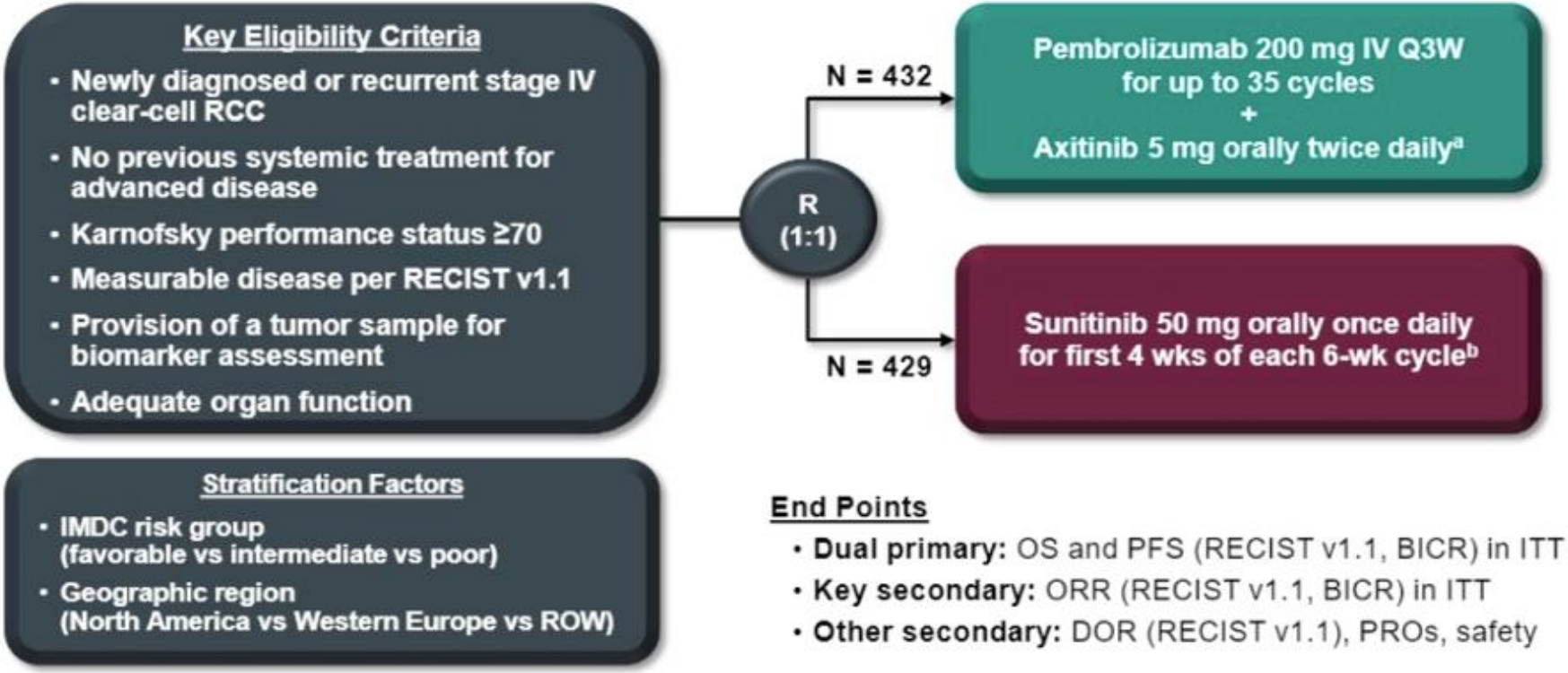
Active surveillance and TKI can be considered in asymptomatic patients with indolent IMDC good prognosis MRCC (II, C)

KEYNOTE-426 Study Design

IO + VEGF



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

[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity.
[b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 wks of each 6-wk cycle to manage toxicity.
BICR, blinded independent central radiologic review; DOR, duration of response; PROs, patient-reported outcomes; ROW, rest of world.
KEYNOTE-426 is a randomized, open-label, phase 3 study (ClinicalTrials.gov identifier NCT02853331).

Baseline Characteristics

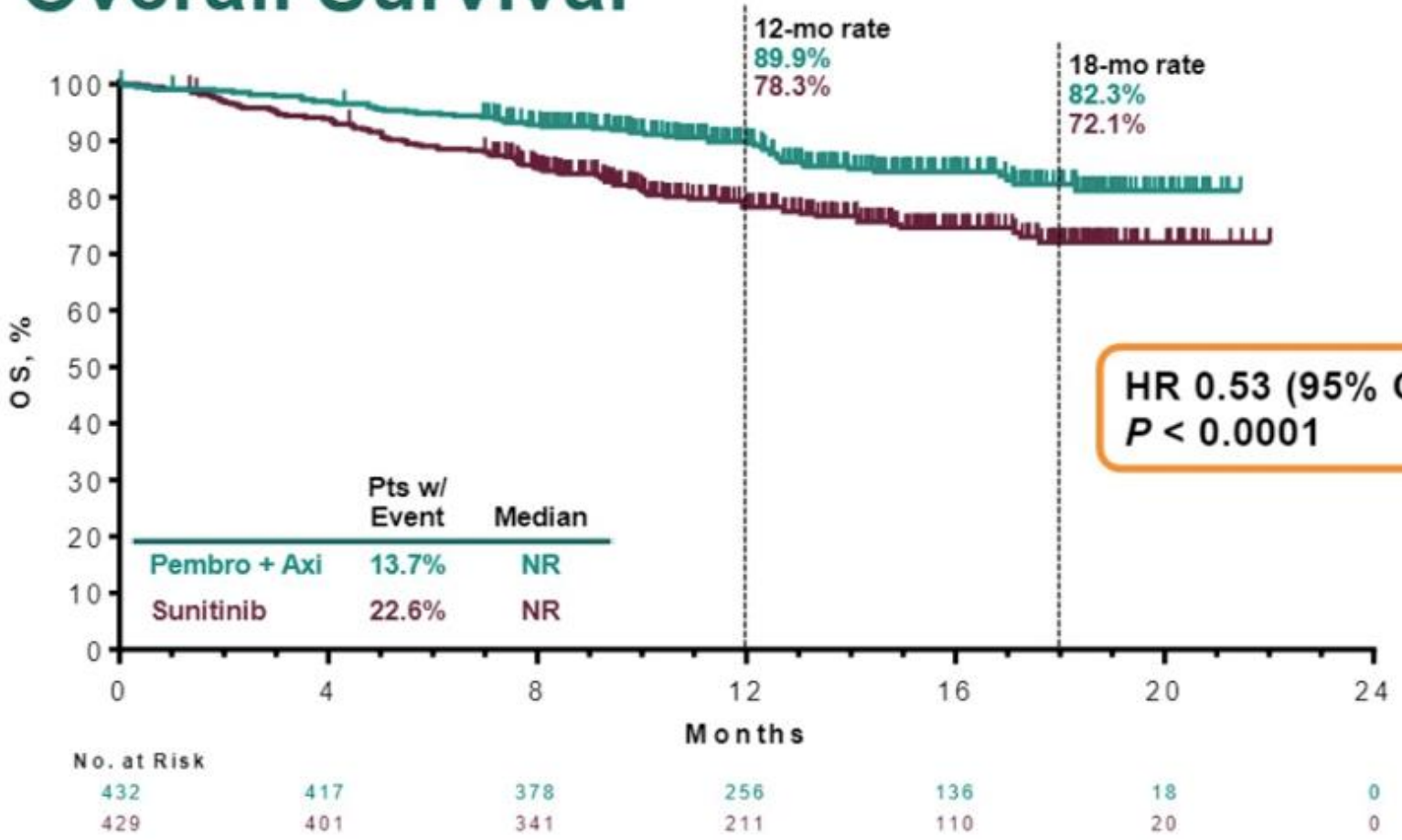
IO + VEGF

	Pembrolizumab + Axitinib N = 432	Sunitinib N = 429
Age, median (range)	62 yrs (30-89)	61 yrs (26-90)
Male	308 (71.3%)	320 (74.6%)
Region of enrollment		
North America	104 (24.1%)	103 (24.0%)
Western Europe	106 (24.5%)	104 (24.2%)
Rest of world	222 (51.4%)	222 (51.7%)
IMDC risk category		
Favorable	138 (31.9%)	131 (30.5%)
Intermediate	238 (55.1%)	246 (57.3%)
Poor	56 (13.0%)	52 (12.1%)
Sarcomatoid features	51/285 (17.9%)	54/293 (18.4%)
PD-L1 CPS ≥1[a]	243/410 (59.3%)	254/412 (61.7%)
≥2 metastatic organs	315 (72.9%)	331 (77.2%)
Previous nephrectomy	357 (82.6%)	358 (83.4%)

[a]Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay. CPS = combined positive score = number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100.
Data cutoff date: Aug 24, 2018.

IO + VEGF

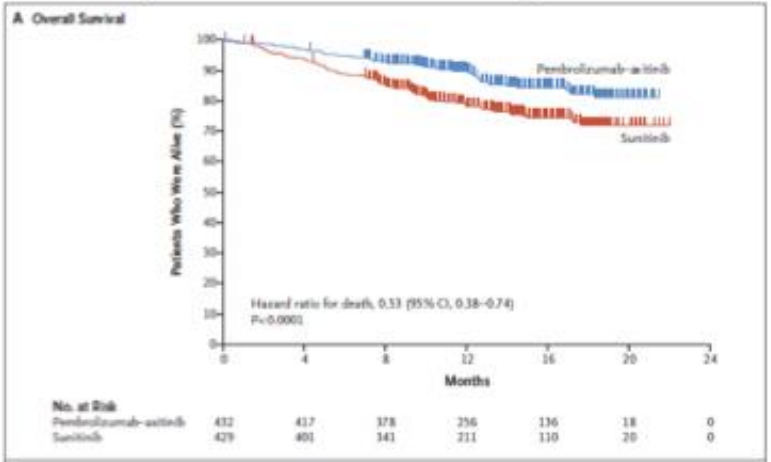
Overall Survival

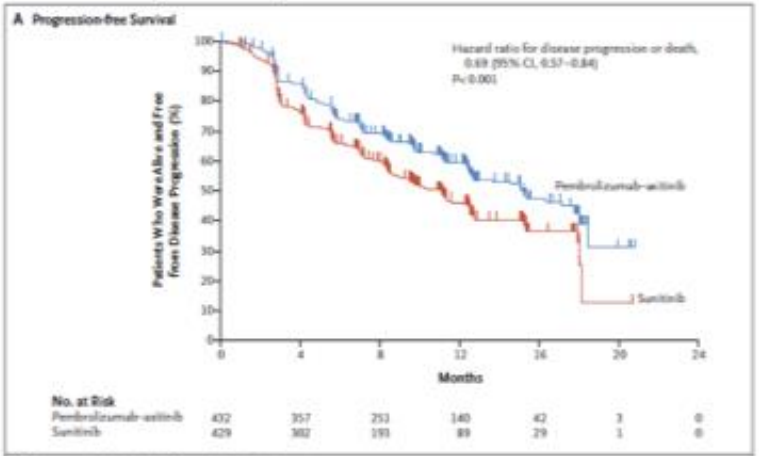


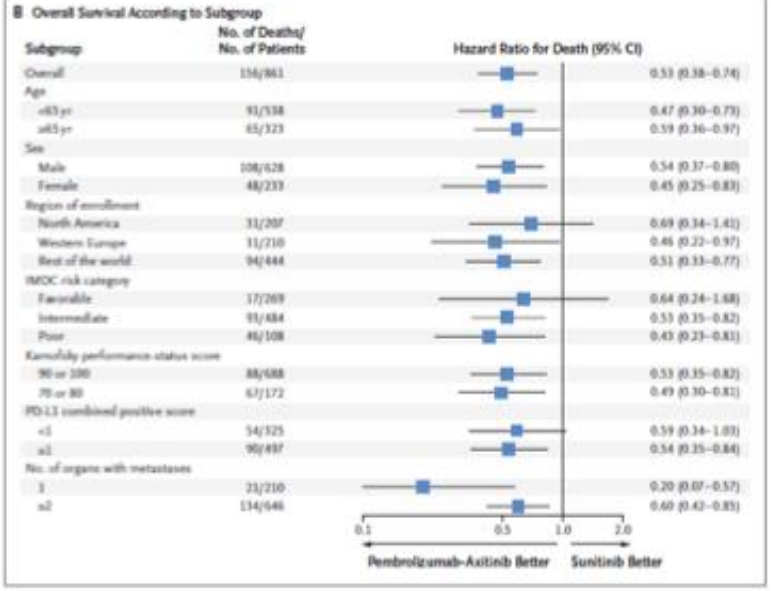
HR 0.53 (95% CI 0.38-0.74)
P < 0.0001

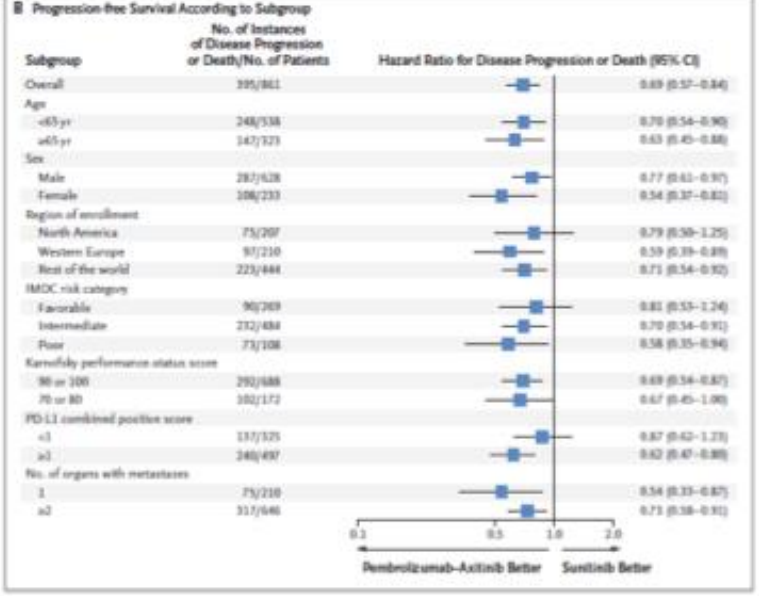
Data cutoff date: Aug 24, 2018.

IO + VEGF


A Overall Survival
Pembrolizumab–axitinib
Sunitinib
Patients Who Were Alive (%)
Hazard ratio for death, 0.53 (95% CI, 0.38–0.74)
P<0.0001
Months
No. at Risk
Pembrolizumab–axitinib 432 417 378 256 136 18 0
Sunitinib 429 401 341 211 110 20 0


A Progression-free Survival
Hazard ratio for disease progression or death, 0.69 (95% CI, 0.57–0.84)
P<0.001
Pembrolizumab–axitinib
Sunitinib
Patients Who Were Alive and Free from Disease Progression (%)
Months
No. at Risk
Pembrolizumab–axitinib 432 357 253 140 42 3 0
Sunitinib 429 382 193 89 29 1 0


B Overall Survival According to Subgroup
Subgroup
No. of Deaths/ No. of Patients
Hazard Ratio for Death (95% CI)
Overall 136/861 0.53 (0.38–0.74)
Age
<65 yr 93/538 0.47 (0.30–0.73)
≥65 yr 65/323 0.59 (0.36–0.97)
Sex
Male 108/628 0.54 (0.37–0.80)
Female 48/233 0.45 (0.25–0.83)
Region of enrollment
North America 31/207 0.69 (0.34–1.41)
Western Europe 31/210 0.46 (0.22–0.97)
Rest of the world 94/444 0.51 (0.33–0.77)
IMDC risk category
Favorable 17/269 0.64 (0.24–1.68)
Intermediate 93/484 0.53 (0.35–0.82)
Poor 46/108 0.43 (0.23–0.81)
Karnofsky performance status score
90 or 100 88/688 0.53 (0.35–0.82)
70 or 80 67/172 0.49 (0.30–0.81)
PD-L1 combined positive score
<1 54/325 0.59 (0.34–1.03)
≥1 90/497 0.54 (0.35–0.84)
No. of organs with metastases
1 23/210 0.20 (0.07–0.57)
≥2 134/646 0.60 (0.42–0.85)
0.1 0.5 1.0 2.0
Pembrolizumab–Axitinib Better
Sunitinib Better


B Progression-free Survival According to Subgroup
Subgroup
No. of Instances of Disease Progression or Death/No. of Patients
Hazard Ratio for Disease Progression or Death (95% CI)
Overall 395/861 0.69 (0.57–0.84)
Age
<65 yr 248/538 0.70 (0.54–0.90)
≥65 yr 147/323 0.63 (0.45–0.88)
Sex
Male 287/628 0.77 (0.61–0.97)
Female 108/233 0.54 (0.37–0.82)
Region of enrollment
North America 75/207 0.79 (0.50–1.25)
Western Europe 97/210 0.59 (0.39–0.89)
Rest of the world 223/444 0.71 (0.54–0.92)
IMDC risk category
Favorable 90/269 0.81 (0.53–1.24)
Intermediate 232/484 0.70 (0.54–0.91)
Poor 73/108 0.58 (0.35–0.94)
Karnofsky performance status score
90 or 100 292/688 0.69 (0.54–0.87)
70 or 80 102/172 0.67 (0.45–1.00)
PD-L1 combined positive score
<1 137/325 0.87 (0.62–1.23)
≥1 240/497 0.62 (0.47–0.80)
No. of organs with metastases
1 75/210 0.54 (0.33–0.87)
≥2 317/646 0.71 (0.58–0.91)
0.1 0.5 1.0 2.0
Pembrolizumab–Axitinib Better
Sunitinib Better

IO + VEGF

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

Response	Pembrolizumab/Axitinib (n = 432)	Sunitinib (n = 429)
ORR, % (95% CI)	59.3 (54.5-63.9)	35.7 (31.1-40.4)
Best overall response, n (%)		
▪ CR	25 (5.8)	8 (1.9)
▪ PR	231 (53.5)	145 (33.8)
▪ SD	106 (24.5)	169 (39.4)
▪ PD	47 (10.9)	73 (17.0)
▪ Not evaluable	8 (1.9)	6 (1.4)
▪ Not assessed	15 (3.5)	28 (6.5)
Median TTR, mos (range)	2.8 (1.5-16.6)	2.9 (2.1-15.1)
Median DoR, mos (range)	NR (1.4-18.2+)	15.2 (1.1-15.4+)

Rini. N Engl J Med 2019;380:1116.

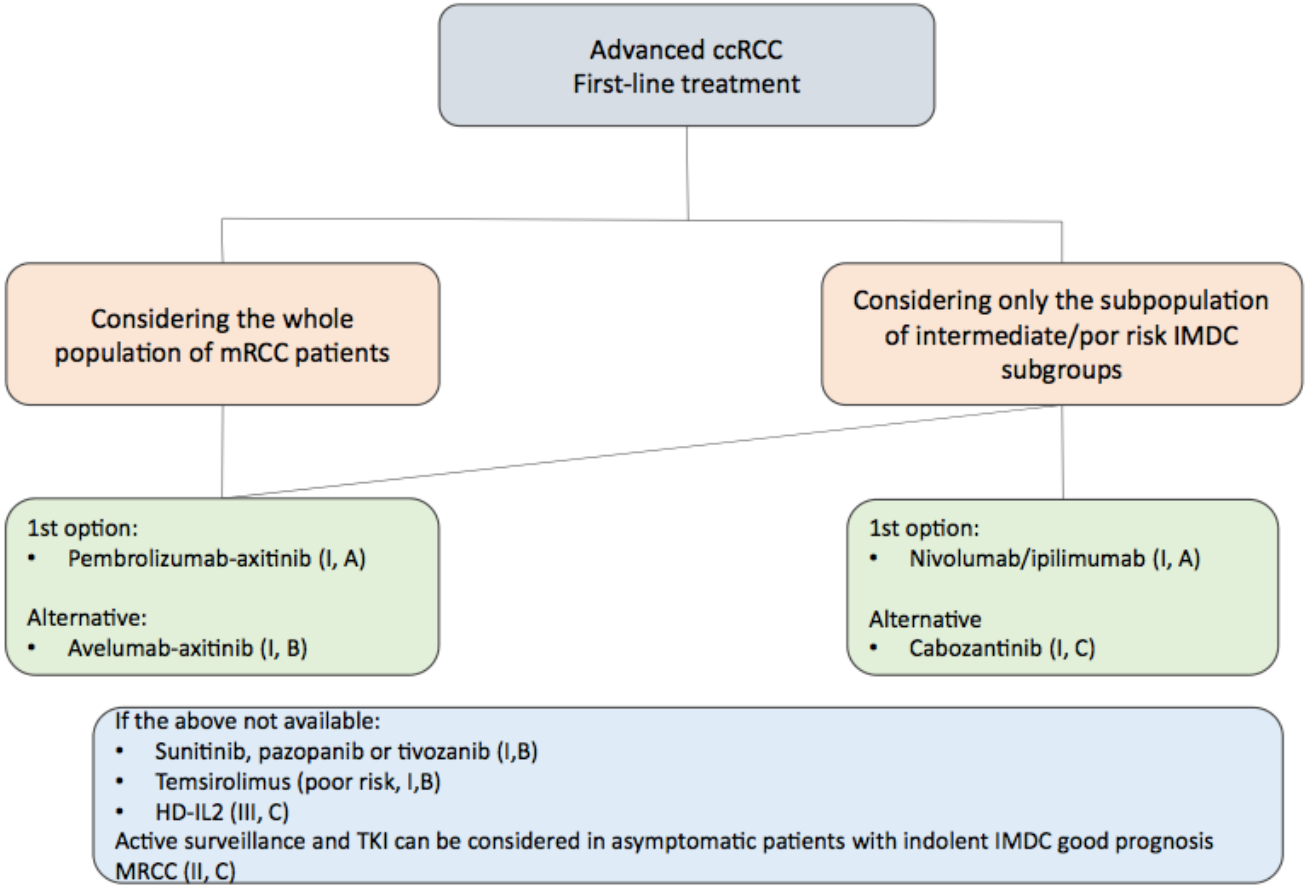
Slide credit: clinicaloptions.com

IO + VEGF

Adverse Events of Interest: Incidence

	Pembro + Axi (N = 429)		Sunitinib (N = 425)	
	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Any	51.3%	10.7%	36.2%	1.9%
Hypothyroidism	35.4%	0.2%	31.5%	0.2%
Hyperthyroidism	12.8%	1.2%	3.8%	0
Adrenal insufficiency	3.0%	0.7%	0.2%	0
Hepatitis	2.8%	2.3%	0.5%	0.2%
Pneumonitis	2.8%	0.5%	0.2%	0
Thyroiditis	2.8%	0.2%	0.5%	0
Colitis	2.6%	1.9%	0.7%	0
Severe skin reactions	1.9%	1.2%	1.4%	0.7%
Infusion reactions	1.6%	0.2%	0.9%[a]	0.2%[a]
Nephritis	1.4%	0.2%	0.2%	0
Hypophysitis	1.2%	0.9%	0	0

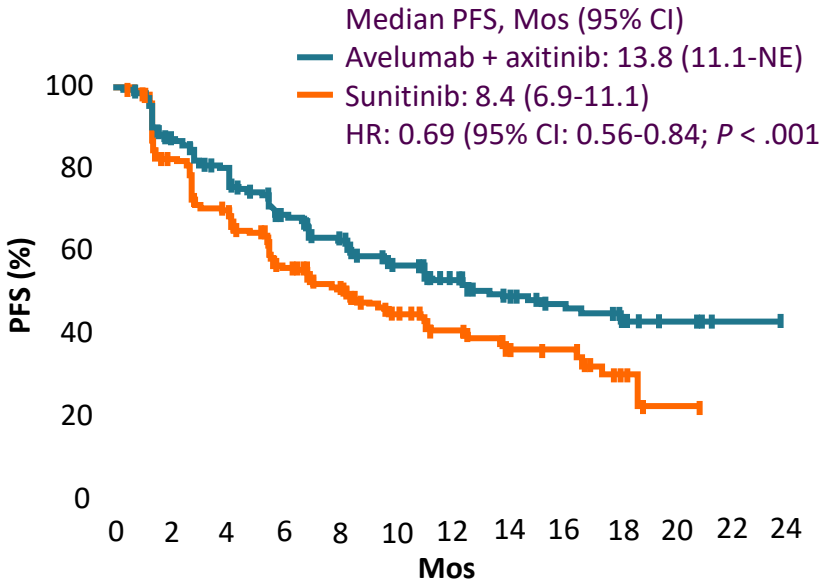
[a]Includes the preferred terms "anaphylactic reaction" and "hypersensitivity," which were experienced by patients in the sunitinib arm.
Events are listed in order of incidence in the pembro + axi arm and are included regardless of attribution to study treatment or immune relatedness by the investigator. The specific events are based on a list of terms specified by the sponsor. In addition to the specific terms listed, related terms were also included. Data cutoff date: Aug 24, 2018.


Advanced ccRCC
First-line treatment
Considering the whole population of mRCC patients
Considering only the subpopulation of intermediate/por risk IMDC subgroups
1st option:
• Pembrolizumab-axitinib (I, A)
Alternative:
• Avelumab-axitinib (I, B)
1st option:
• Nivolumab/ipilimumab (I, A)
Alternative
• Cabozantinib (I, C)
If the above not available:
• Sunitinib, pazopanib or tivozanib (I,B)
• Temsirolimus (poor risk, I,B)
• HD-IL2 (III, C)
Active surveillance and TKI can be considered in asymptomatic patients with indolent IMDC good prognosis MRCC (II, C)

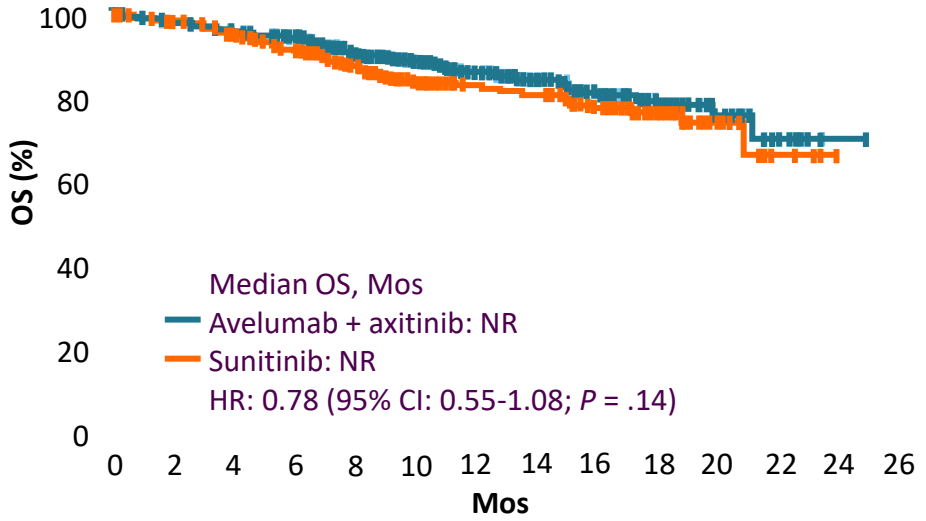
JAVELIN Renal 101: Avelumab + Axitinib in Treatment-Naive Advanced RCC

IO + VEGF

PFS in ITT Population



OS in ITT Population



ALTERNATIVA

Slide credit: clinicaloptions.com

ALTERNATIVA

VEGF

SUNITINIB

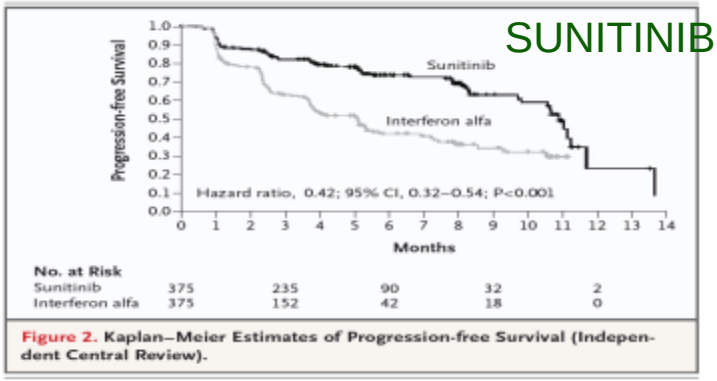
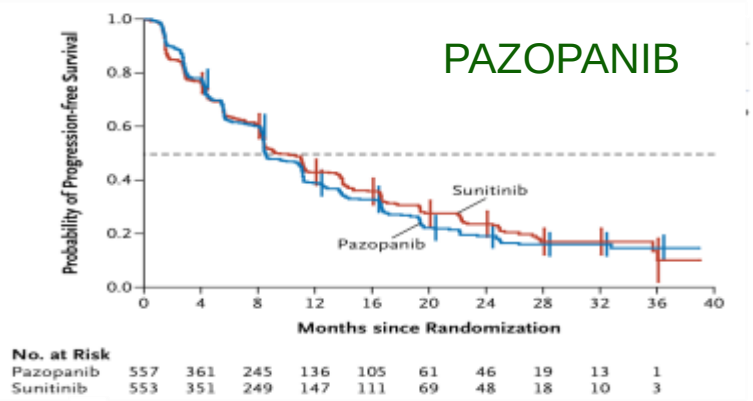
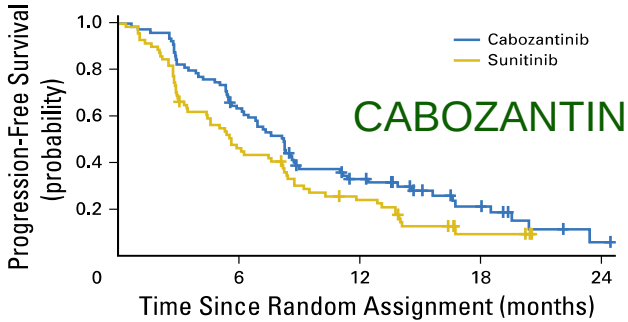


Figure 2. Kaplan–Meier Estimates of Progression-free Survival (Independent Central Review).

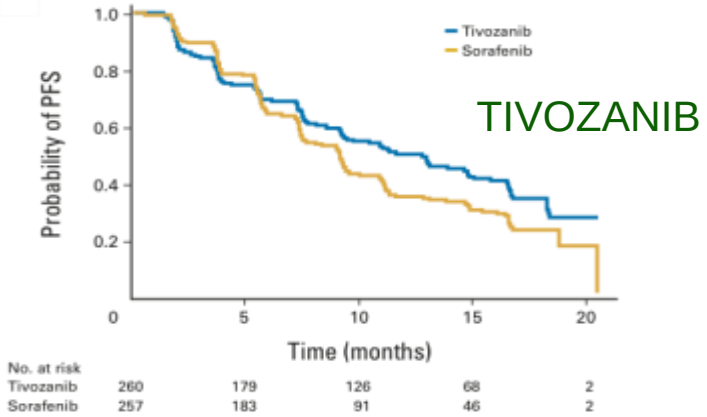
PAZOPANIB



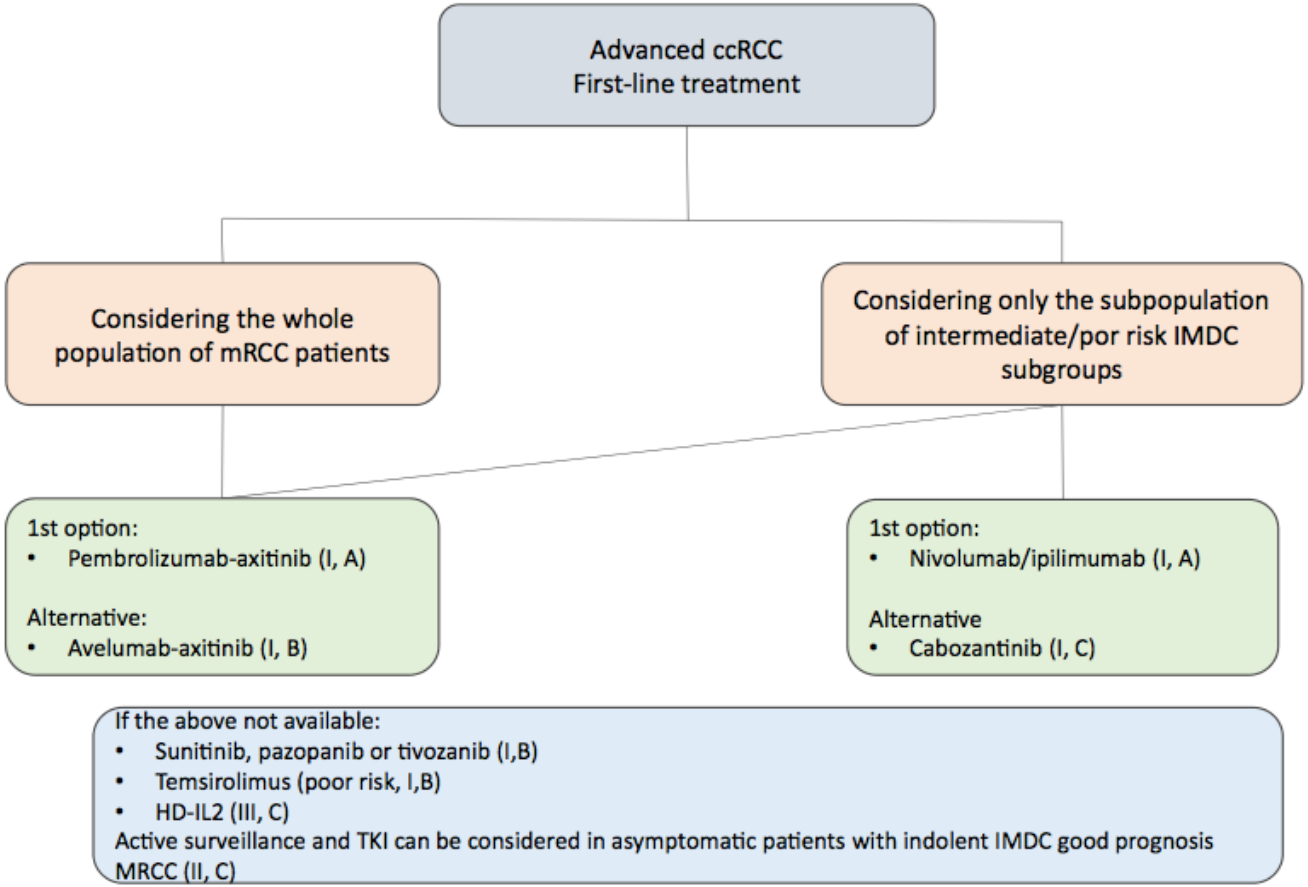
CABOZANTINIB



TIVOZANIB



Motzer RJ, et al. N Engl J Med 2007;356:115-24. Motzer RJ, et al. N Engl J Med 2013;369:722-31
Motzer RJ, et al. J Clin Oncol 2013;31:3791-9. Choueiri TK, et al. J Clin Oncol 2017; 35:591-7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• Temsirolimus (poor risk, I,B)
• HD-IL2 (III, C)
Active surveillance and TKI can be considered in asymptomatic patients with indolent IMDC good prognosis MRCC (II, C)

Prospective, Phase II Observational Study in Patients With Asymptomatic Metastatic RCC

- Patients with clinically evident metastatic RCC of any histologic subtype (N = 52)
- First documentation (radiographic or histologic) of metastatic RCC up to 12 months prior to registration on study
- No prior systemic therapy for RCC in the metastatic or neo/adjuvant setting
- Prior XRT (including for CNS metastases) and prior nephrectomy/metastasectomy permitted but not required
- No disease-related symptoms
- Measurable/evaluable disease per RECIST v1.0

CT every 3 mos in Yr 1, every 4 mos in Yr 2, then every 6 mos

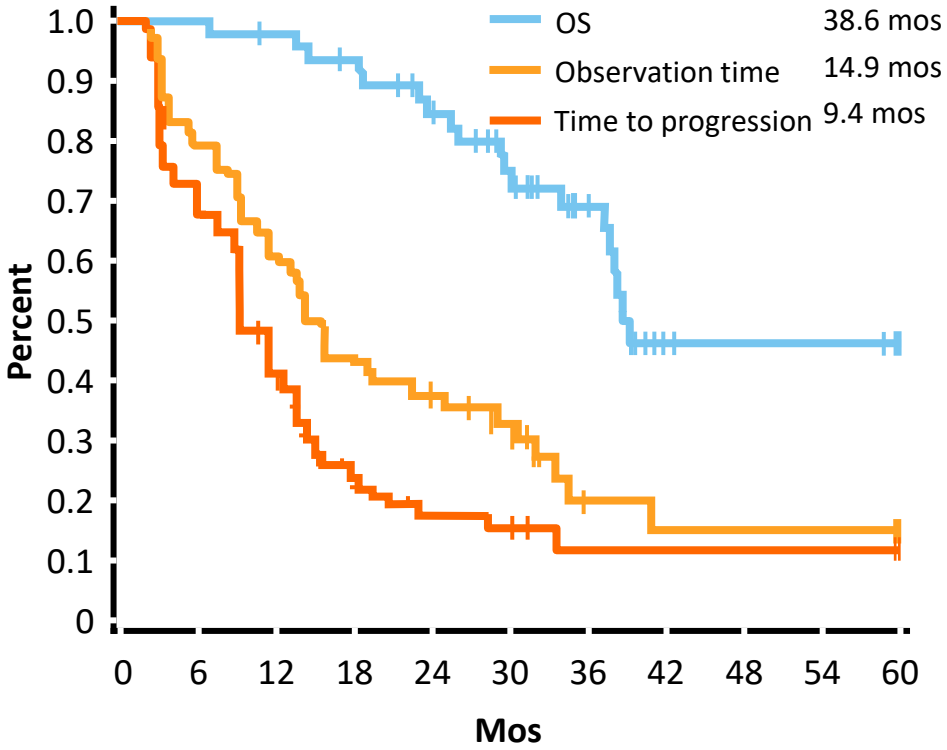
Initiation of systemic treatment per doctor/ patient discretion

- FKSI-DRS (QoL) and HADS (anxiety/depression) assessments administered at baseline and at every CT scan timepoint
- Peripheral blood for immune cell quantification drawn at baseline and at every CT scan time point

Rini. Lancet Oncol. 2016;17:1317.

Slide credit: clinicaloptions.com

Prospective Observation Study: Outcomes



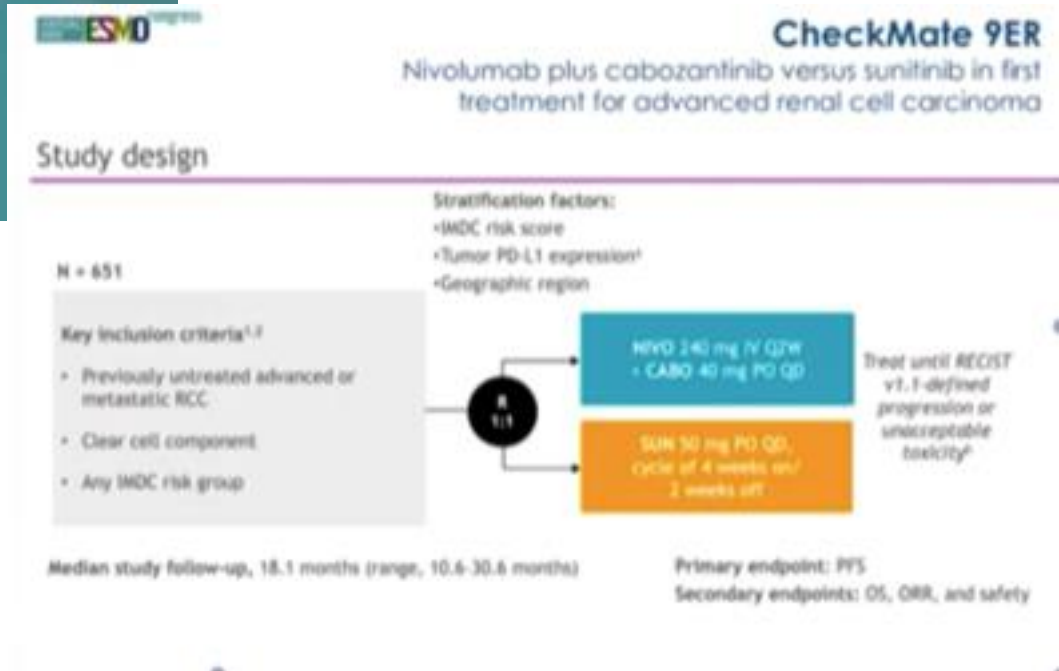
- Median absolute change in tumor burden during surveillance: 1.3 cm
  - Relative change: 31%
  - Median growth rate: 0.09 cm/mo
- 23/43 (53%) patients with progressive disease immediately started systematic therapy after progression and 20/43 (47%) continued on surveillance
  - Median additional surveillance period for these patients: 15.8 mos

Rini. Lancet Oncol. 2016;17:1317.

Slide credit: clinicaloptions.com

Nivolumab + cabozantinib vs sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial

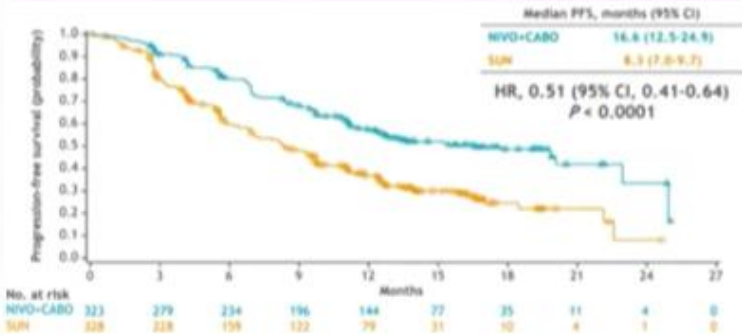
(6960, Toni Choueiri)



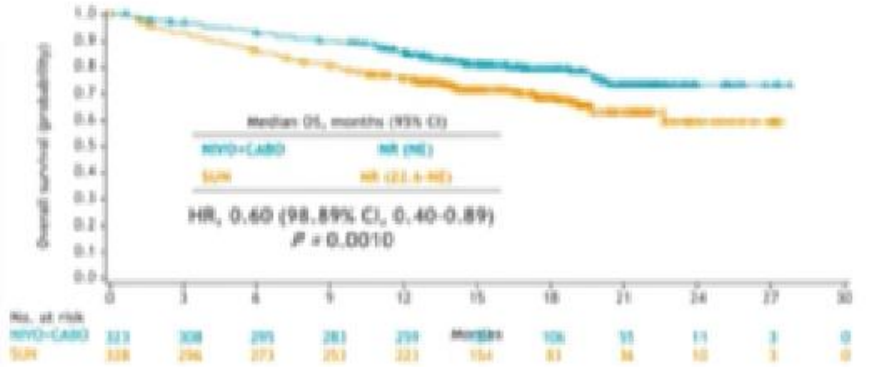
CheckMate 9ER

Nivolumab plus cabozantinib versus sunitinib in first treatment for advanced renal cell carcinoma

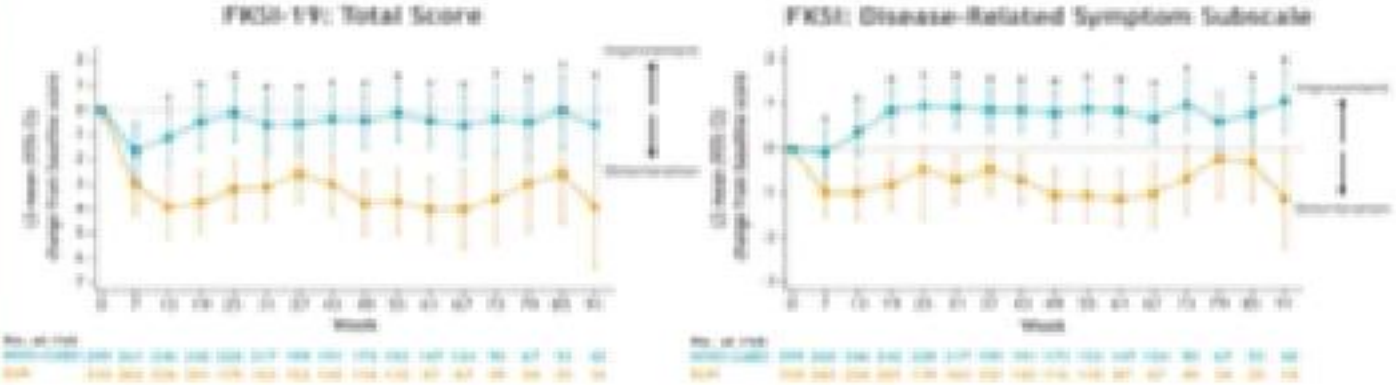
Progression-free survival per BICR



Overall survival



Health-related quality of life



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- CONCLUSIONES

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

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

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• Cabozantinib (category 1) • Nivolumab[b] (category 1) • Ipilimumab + nivolumab[b]	• Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab[b] • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab[b] (category 3)	• Bevacizumab[f] (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B)

JULIO 2020

CABOZANTINIB
NIVOLUMAB
NIVO-IPI

} Categoría 1

ENSAYOS EN 2ª Y SUCESIVAS LÍNEAS EN RCC
Características y eficacia

Study	RECORD-1[1]		INTORSECT[2]		AXIS[3,4]		HOPE-205[5]			METEOR[6]		CHECKMATE 025[7]	
Tx Arms	E	Pl	Tem	So	Ax	So	L/E	L	E	Cabo	E	Nivo	E
Phase	III		III		III		II			III		III	
Line of Tx	> 2nd		2nd		2nd		2nd			> 2nd		2nd-3rd	
Previous Tx	At least Su and/or So		Su		Su or Bev-IFN or Tem or cytokines		VEGF-targeted			At least one VEGF-targeted		VEGF-targeted	
Histology	Clear cell		Any (82% clear cell)		Clear cell		Clear cell			Clear cell		Clear cell	
Primary endpoint	PFS		PFS		PFS		PFS			PFS		OS	
N	272	138	259	253	361	362	51	52	50	330	328	410	411
Risk groups (G/I/P)	29/56/15		18/70/12		28/37/33		23/37/40			46/41/13		36/49/15	
ORR (%)	1.8	0	8	8	19	9	43	27	6	17	3	25	5
PFS (mo)	4.9	1.9	4.3	3.9	6.7	4.7	14.6	7.4	5.5	7.4	3.8	4.6	4.4
PFS – HR (95% CI)	0.33 (0.25-0.43)		0.87 (0.71-1.07)		0.67 (0.54-0.81)		0.40 (L/E vs. E), 0.66 (L/E vs. L), 0.61 (L vs. E)			0.58 (0.45-0.75)		0.88 (0.75-1.03)	
OS (mo)	14.8	14.4	12.27	16.64	20.1	19.2	25.5	18.4	17.5	21.4	16.5	25.0	19.6
OS – HR (95% CI)	0.87 (0.65-1-15)		1.31 (1.05-1.63)		0.97 (0.80-1.17)		0.51 (L/E vs. E), 0.75 (L/E vs. L), 0.68 (L vs. E)			0.66 (0.53-0.83)		0.73 (0.57-0.93)	

[1]Motzer RJ, et al. Cancer 2010;116:4256–4265. [2]Hutson TE, et al.. J Clin Oncol 2013;32:760-767.[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]Choueiri TK, et al. N Engl J Med 2015;373:1814-1823.
[7]Motzer RJ, et al. N Engl J Med 2015;373:1803-1813.

ENSAYOS EN 2ª Y SUCESIVAS LÍNEAS EN RCC
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Tx Arms	E	Pl	Tem	So	Ax	So	L/E	L	E	Cabo	E	Nivo	E
Phase	III		III		III		II			III		III	
Line of Tx	> 2nd		2nd		2nd		2nd			> 2nd		2nd-3rd	
Previous Tx	At least Su and/or So		Su		Su or Bev-IFN or Tem or cytokines		VEGF-targeted			At least one VEGF-targeted		VEGF-targeted	
Histology	Clear cell		Any (82% clear cell)		Clear cell		Clear cell			Clear cell		Clear cell	
Primary endpoint	PFS		PFS		PFS		PFS			PFS		OS	
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ORR (%)	1.8	0	8	8	19	9	43	27	6	17	3	25	5
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PFS – HR (95% CI)	0.33 (0.25-0.43)		0.87 (0.71-1.07)		0.67 (0.54-0.81)		0.40 (L/E vs. E), 0.66 (L/E vs. L), 0.61 (L vs. E)			0.58 (0.45-0.75)		0.88 (0.75-1.03)	
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OS – HR (95% CI)	0.87 (0.65-1-15)		1.31 (1.05-1.63)		0.97 (0.80-1.17)		0.51 (L/E vs. E), 0.75 (L/E vs. L), 0.68 (L vs. E)			0.66 (0.53-0.83)		0.73 (0.57-0.93)	

[1]Motzer RJ, et al. Cancer 2010;116:4256–4265. [2]Hutson TE, et al.. J Clin Oncol 2013;32:760-767.[3]Rini BI, et al. Lancet 2011;378:1931–1939.
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SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• Cabozantinib (category 1) • Nivolumab[b] (category 1) • Ipilimumab + nivolumab[b]	• Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab[b] • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab[b] (category 3)	• Bevacizumab[f] (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

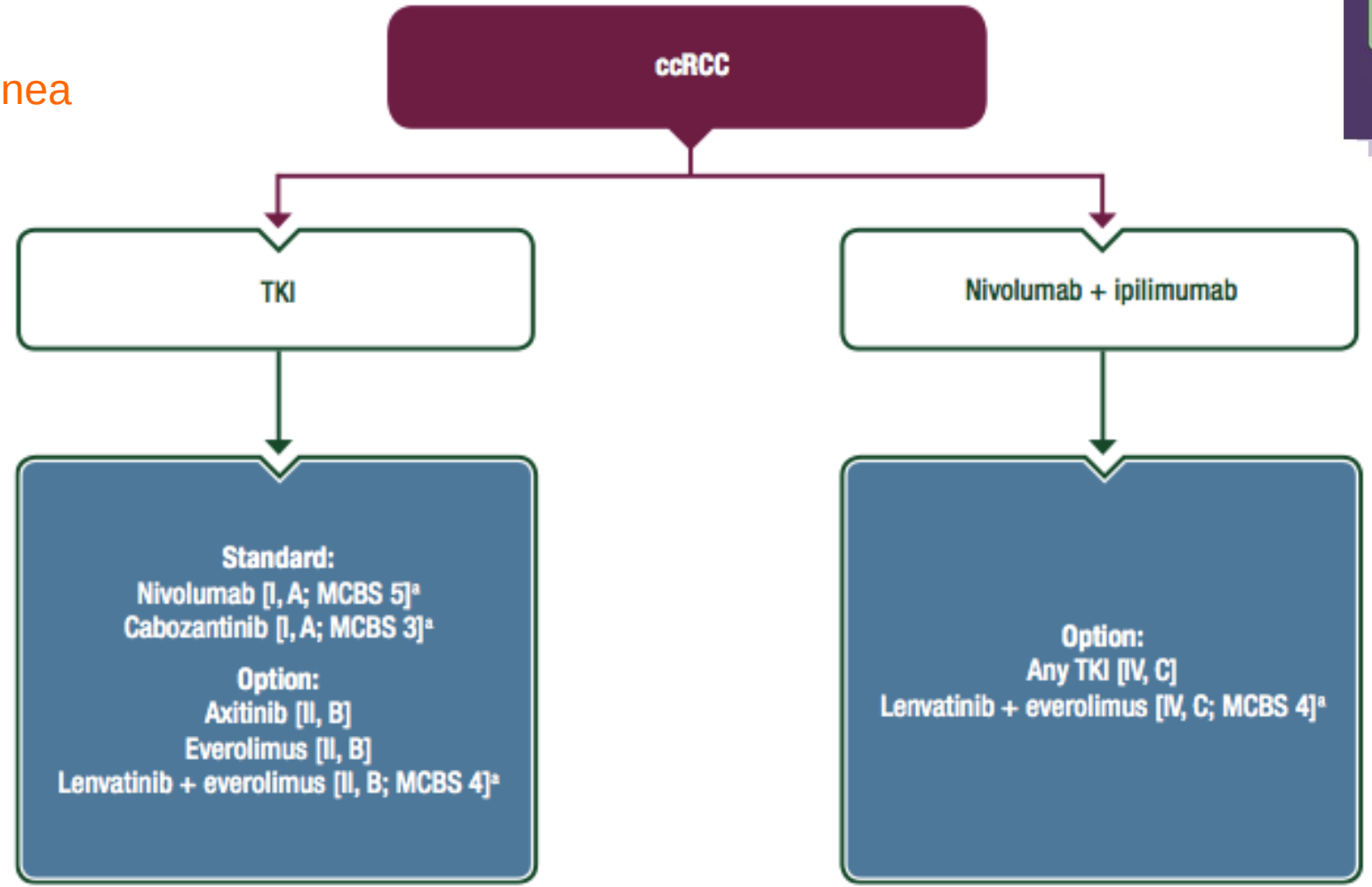
Annals of Oncology 30: 706–720, 2019
doi:10.1093/annonc/mdz056
Published online 21 February 2019

SPECIAL ARTICLE

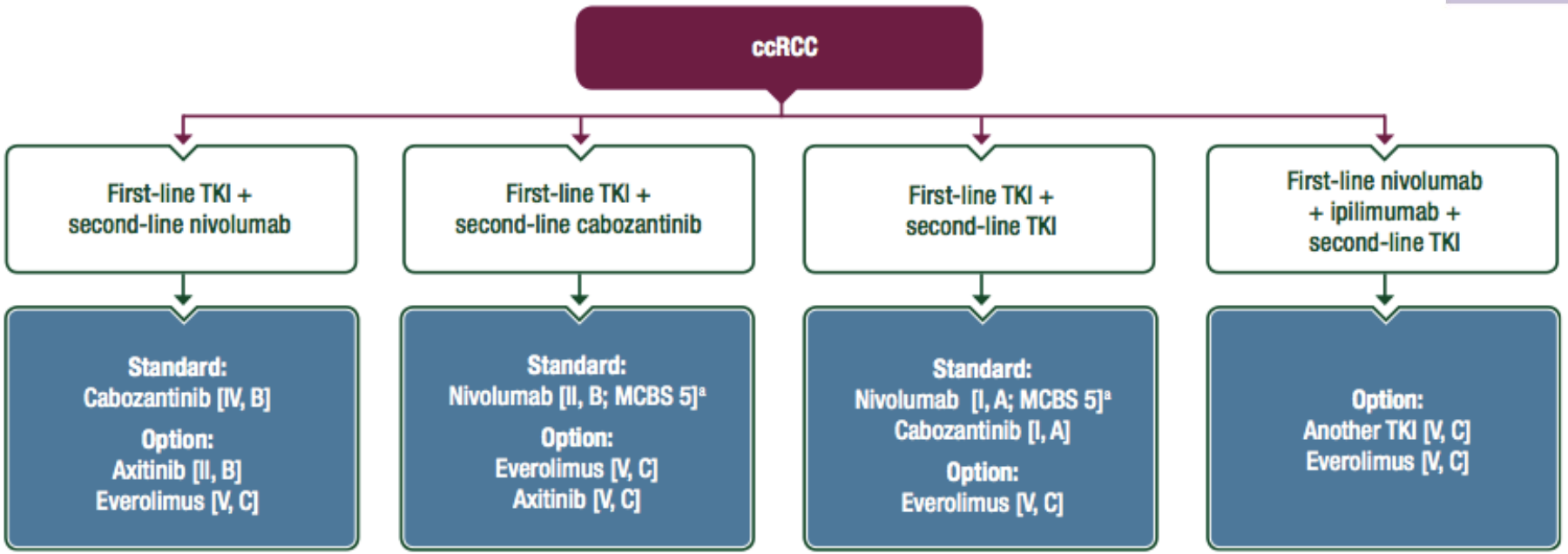
Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

B. Escudier[1], C. Porta[2,3], M. Schmidinger[4], N. Rioux-Leclercq[5], A. Bex[6,7], V. Khoo[8,9], V. Grünwald[10]

2º linea


ccRCC
TKI
Nivolumab + ipilimumab
Standard:
Nivolumab [I, A; MCBS 5]a
Cabozantinib [I, A; MCBS 3]a
Option:
Axitinib [II, B]
Everolimus [II, B]
Lenvatinib + everolimus [II, B; MCBS 4]a
Option:
Any TKI [IV, C]
Lenvatinib + everolimus [IV, C; MCBS 4]a

3º linea


ccRCC
First-line TKI + second-line nivolumab
First-line TKI + second-line cabozantinib
First-line TKI + second-line TKI
First-line nivolumab + ipilimumab + second-line TKI
Standard: Cabozantinib [IV, B]
Option: Axitinib [II, B] Everolimus [V, C]
Standard: Nivolumab [II, B; MCBS 5][a]
Option: Everolimus [V, C] Axitinib [V, C]
Standard: Nivolumab [I, A; MCBS 5][a] Cabozantinib [I, A]
Option: Everolimus [V, C]
Option: Another TKI [V, C] Everolimus [V, C]

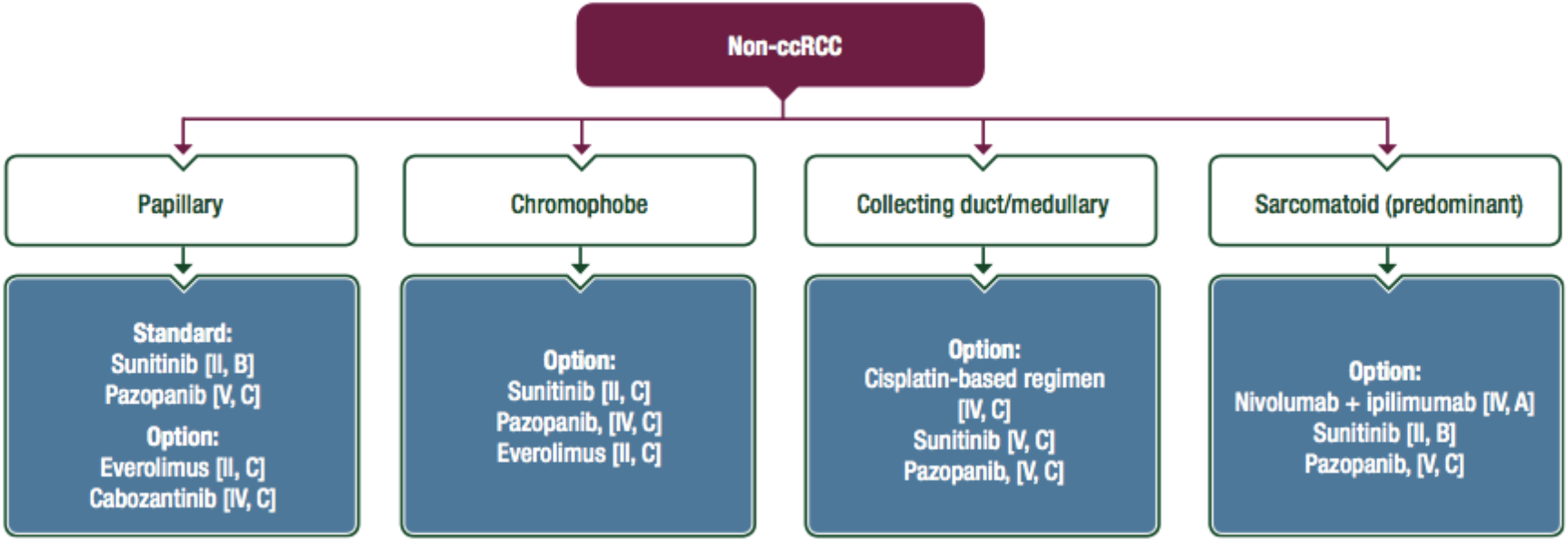


Figure 4. Systemic first-line treatment of non-ccRCC.
Non-ccRCC, non-clear cell renal cell carcinoma.

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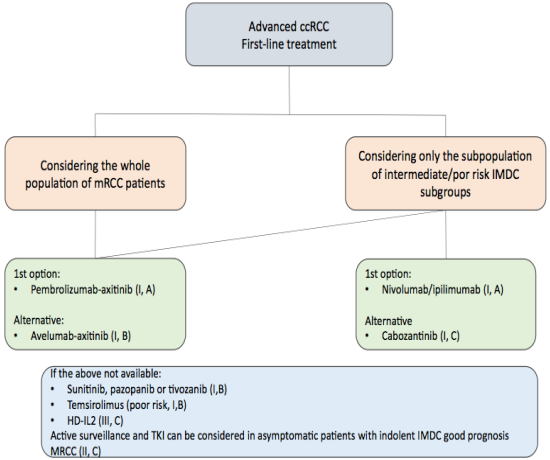
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Alternative:
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Alternative
• Cabozantinib (I, C)
If the above not available:
• Sunitinib, pazopanib or tivozanib (I,B)
• Temsirolimus (poor risk, I,B)
• HD-IL2 (III, C)
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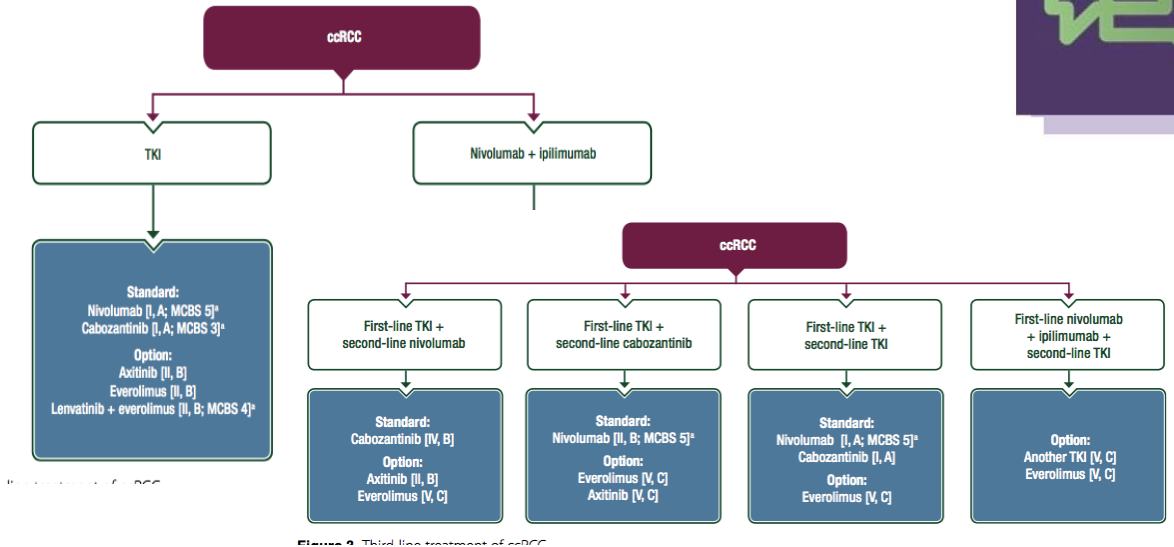
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Nivolumab + ipilimumab
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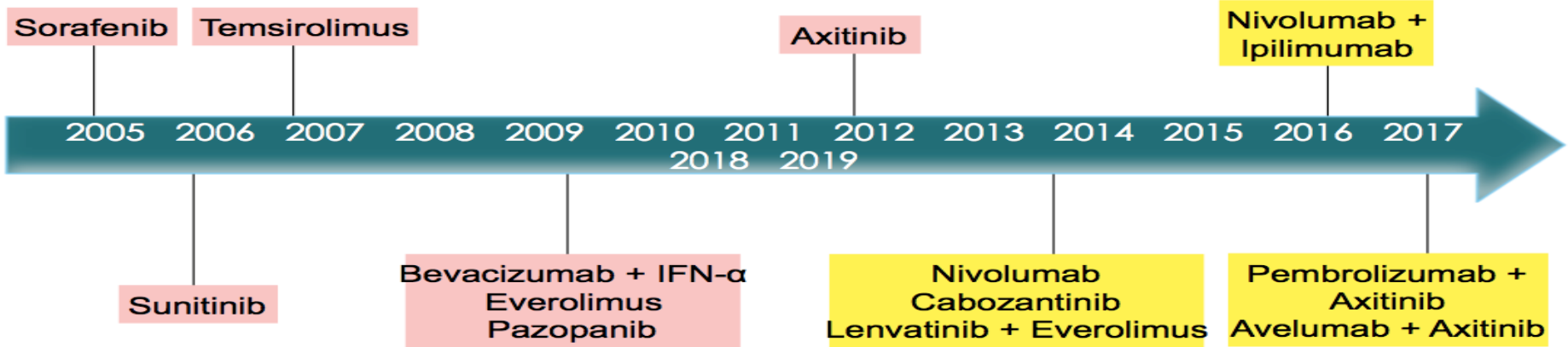
Nivolumab [I, A; MCBS 5]a
Cabozantinib [I, A; MCBS 3]a
Option:
Axitinib [II, B]
Everolimus [II, B]
Lenvatinib + everolimus [II, B; MCBS 4]a
ccRCC
First-line TKI + second-line nivolumab
First-line TKI + second-line cabozantinib
First-line TKI + second-line TKI
First-line nivolumab + ipilimumab + second-line TKI
Standard:
Cabozantinib [IV, B]
Option:
Axitinib [II, B]
Everolimus [V, C]
Standard:
Nivolumab [II, B; MCBS 5]a
Option:
Everolimus [V, C]
Axitinib [V, C]
Standard:
Nivolumab [I, A; MCBS 5]a
Cabozantinib [I, A]
Option:
Everolimus [V, C]
Option:
Another TKI [V, C]
Everolimus [V, C]


Sorafenib
Temsirolimus
Axitinib
Nivolumab + Ipilimumab
2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019
Sunitinib
Bevacizumab + IFN-α
Everolimus
Pazopanib
Nivolumab
Cabozantinib
Lenvatinib + Everolimus
Pembrolizumab + Axitinib
Avelumab + Axitinib

DISCUSIÓN

IO/IO vs IO/TKI

IO/IO	IO/TKI
PROS	**PROS**
Supervivencia global Seguimiento a largo plazo Respuestas duraderas/plateau Posibilidad de suspender terapia	Supervivencia global Mayor PFS Mayor Tasa Respuestas Menor % irAE (15%)
CONTRAS	**CONTRAS**
Mayor % irAE (30%) AE no predecibles Menor PFS/ Tasa Respuestas	Seguimiento inmaduro, ¿beneficio a largo plazo? Importancia cada componente mantenimiento Toxicidad TKI