XXIV Simposio de Revisiones en Cáncer

"Tratamiento médico del cáncer en el año 2022"

PRIMERA LÍNEA EN CÁNCER RENAL AVANZADO: EFICACIA Y MANEJO IO/TKI

Dra Cristina Suárez
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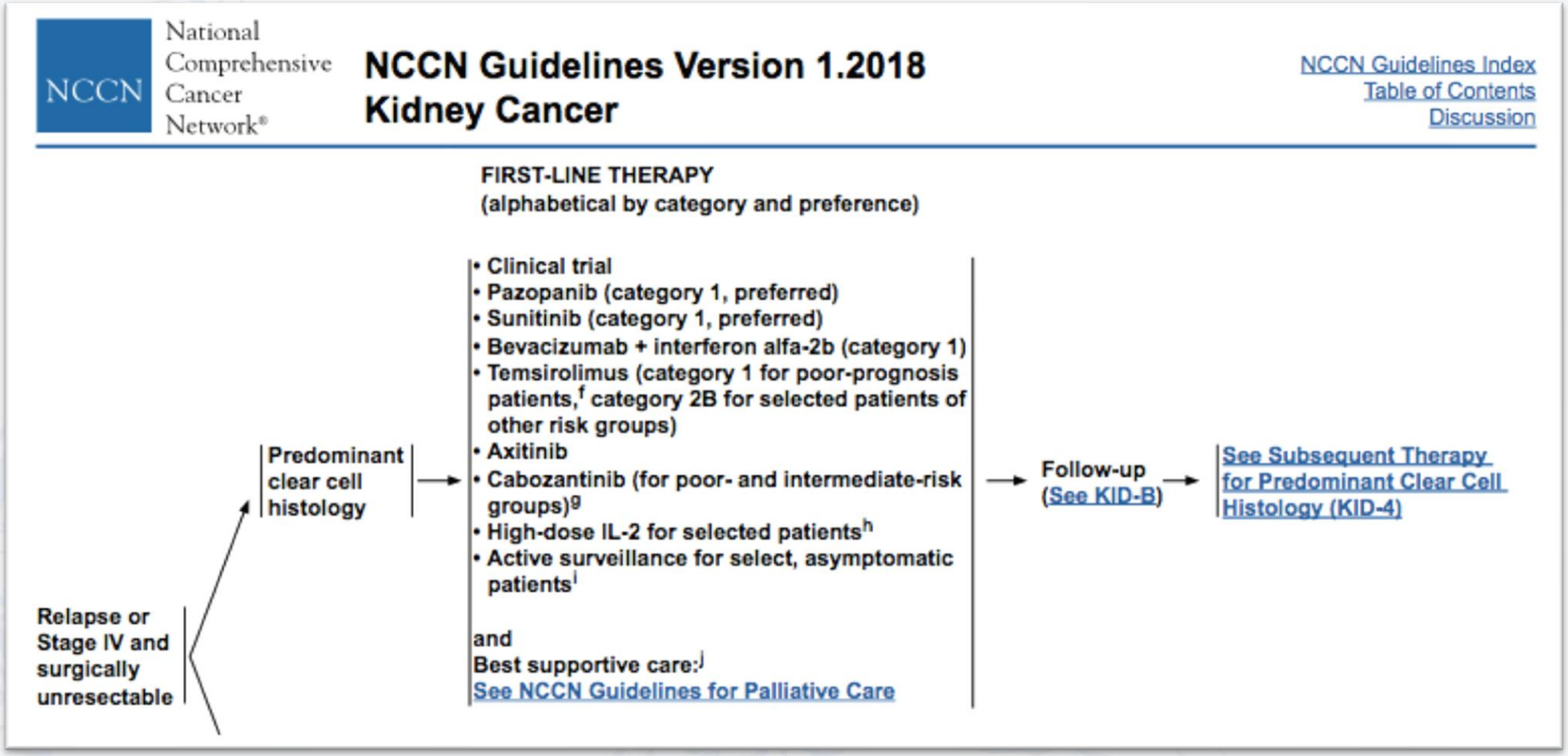
Vall d´Hebron Institute of Oncology

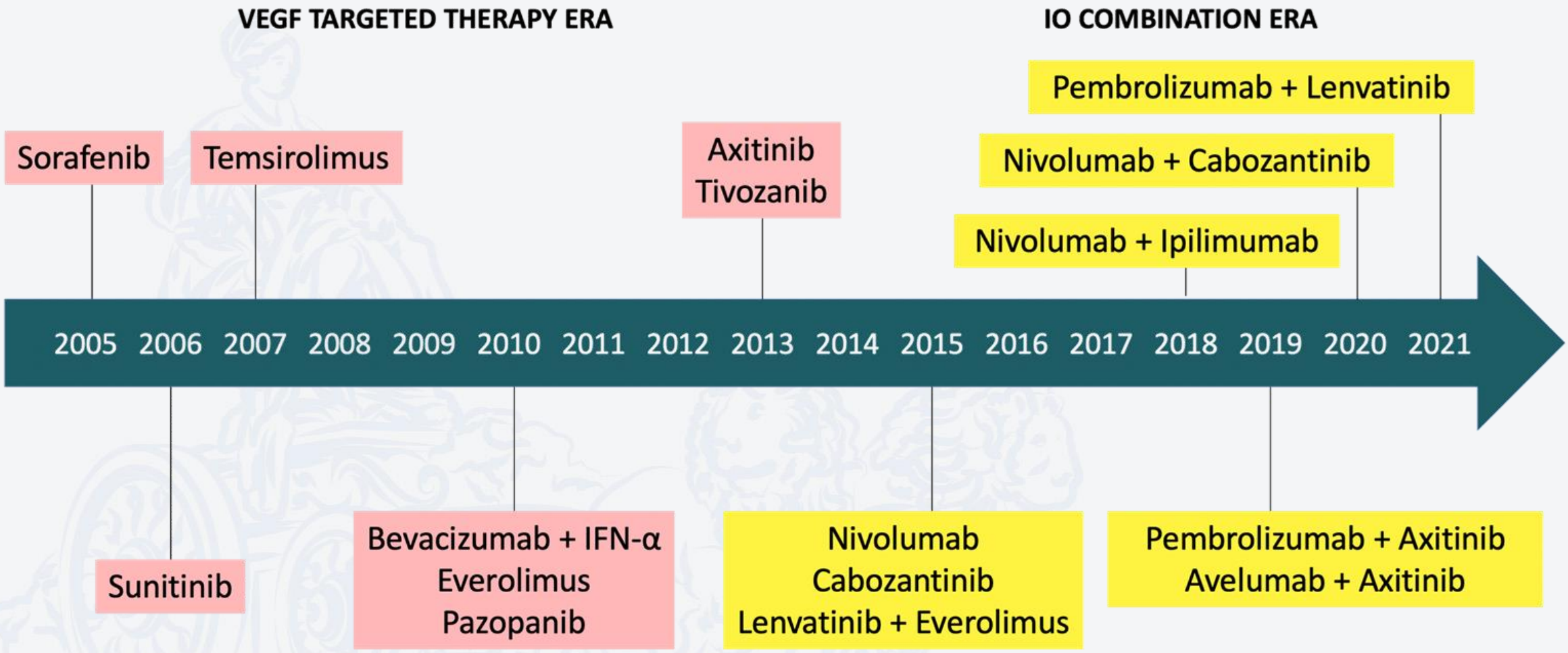
DISCLOSURES

- **Personal financial interests:** Astellas, Atrazeneca, Bayer, BMS, Eusa, Ipsen, Novartis, Pfizer,Sanofi-Aventis, Roche, Merck Sharp & Dohme Corp.
- **Institutional financial interests**: AB Science, Aragon Pharmaceuticals, Arog Pharmaceuticals, INC, Astellas Pharma., Astrazeneca AB, Aveo Pharmaceuticals INC, Bayer AG, Blueprint Medicines Corporation, BN Immunotherapeutics INC, Boehringer Ingelheim España, S.A., Bristol-Myers Squibb International Corporation (BMS), Clovis Oncology, INC, Cougar Biotechnology INC, Deciphera Pharmaceuticals LLC, Exelixis INC, F. Hoffmann-La Roche LTD, Genentech INC, Glaxosmithkline, SA, Incyte Corporation, Janssen-Cilag International NV, Karyopharm Therapeutics INC., Laboratoires Leurquin Mediolanum SAS, Lilly, S.A., Medimmune, Millennium Pharmaceuticals, INC., Nanobiotix SA, Novartis Farmacéutica, S.A., Pfizer, S.L.U, Puma Biotechnology, INC, Sanofi-Aventis, S.A., SFJ Pharma LTD. II, Teva Pharma S.L.U.
- **Non-financial interests**: Steering Comiittee Roche, Steering Comiittee BM

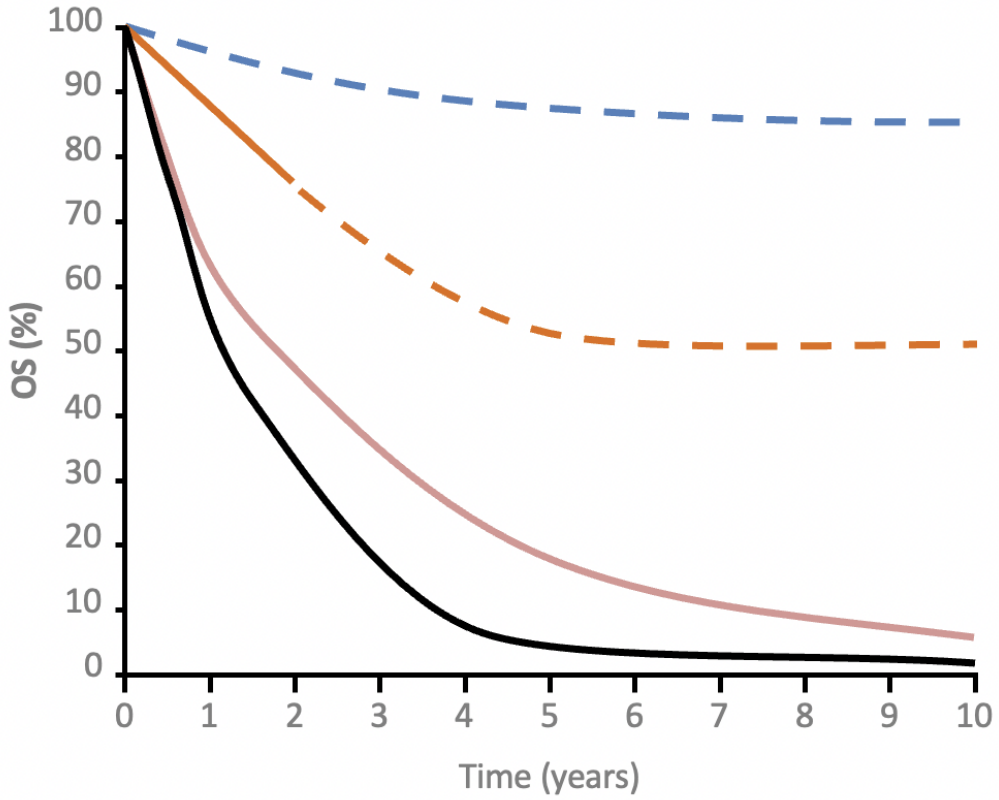
FIRST-LINE THERAPY IN METASTATIC RENAL CELL CARCINOMA IN THE PAST



THERAPEUTIC LANDSCAPE IN MET RENAL CELL CARCINOMA



TARGETED THERAPIES HAVE IMPROVED OS IN mRCC
The "Golden Age"



- **Diamond age (>2025):** The ultimate goal is that >80% of patients with metastatic clear cell RCC will achieve long-term survival
- **Golden age (2015–2025):** Introduction of a number of new drugs
  - ~50% patients achieving durable remissions by 2025 (median survival ~5 years)

1st line:
Tivozanib[2]
Cabozantinib[3]
Nivolumab/ipilimumab
Axitinib/Pembrolizumab
Axitinib/Avelumab
Lenvatinib/Pembrolizumab

- **Modern age (2005–2015):** Seven additional regimens gained approval (median survival to ~30 months)

1st line:
Sunitinib
Pazopanib
Bevacizumab/interferon

- **Dark age (<2005):** Two drugs available to treat aRCC (median survival ~15 months)

IL-2 and/or interferon[1]

ADAPTED FROM Hsieh JJ, et al. Nat Rev Dis Prim 2017;3:17009

FIRST-LINE THERAPY IN METASTATIC RENAL CELL CARCINOMA IN 2022

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Kidney Cancer

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

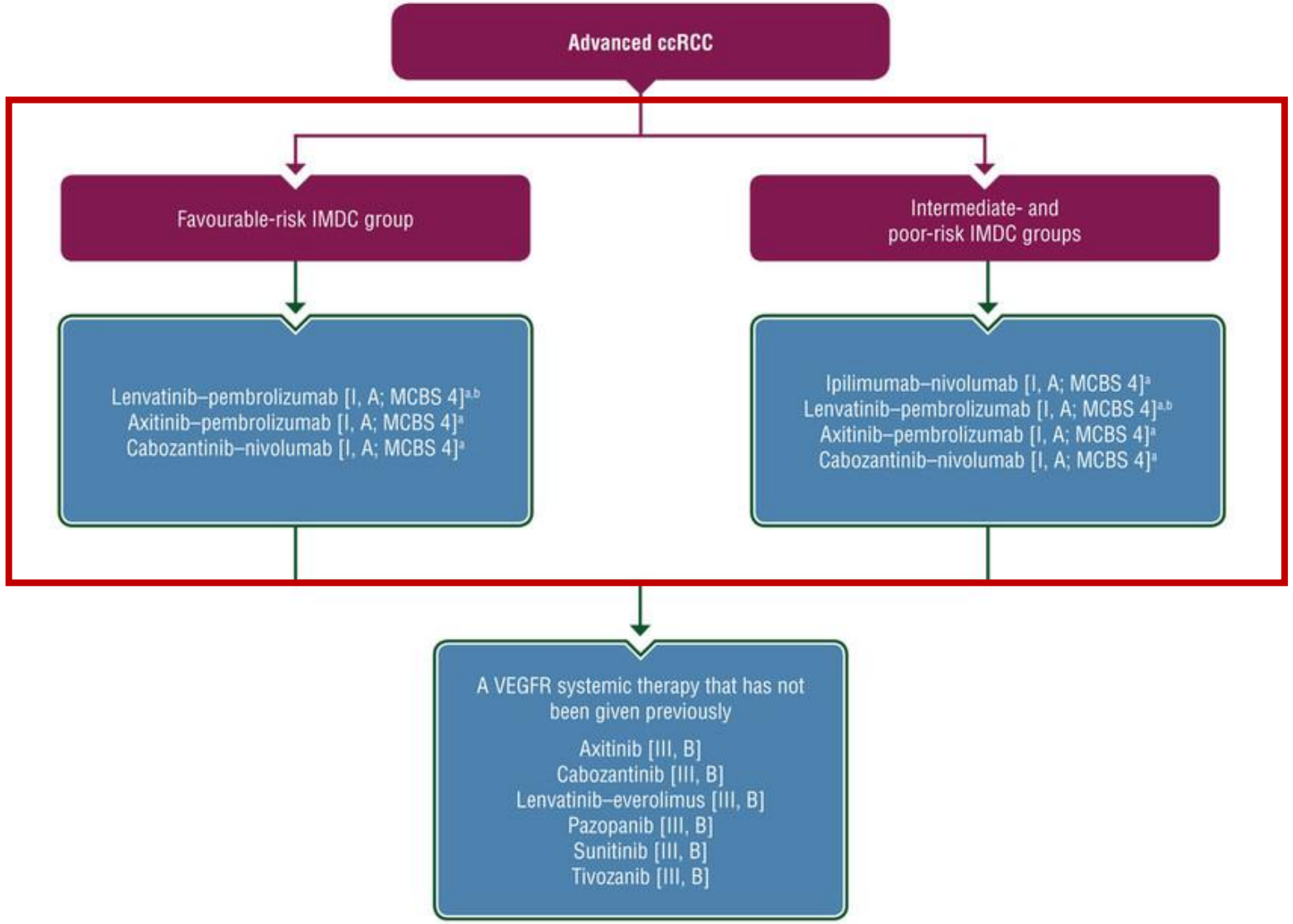
Risk	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1)	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Ipilimumab + nivolumab[b] • Pazopanib • Sunitinib	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d] (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Ipilimumab + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B) • High-dose IL-2[d] (category 3) • Temsirolimus[e] (category 3)

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Cabozantinib (category 1) • Lenvatinib + everolimus (category 1) • Nivolumab[b] (category 1)	• Axitinib (category 1) • Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Tivozanib[g] • Axitinib + avelumab[b] (category 3)	• Everolimus • Bevacizumab[f] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Sorafenib (category 3) • Temsirolimus[e] (category 2B)

https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

2021 ESMO GUIDELINES UPDATE



https://www.esmo.org/guidelines/genitourinary-cancers/renal-cell-carcinoma/eupdate-renal-cell-carcinoma-treatment-recommendations-4

FIRST-LINE COMBINATIONS IN mRCC

- Ipilimumab + Nivolumab (CHECKMATE 214)

IO + IO

- Atezolizumab + Bevacizumab (IMMOTION 151)
- Avelumab + Axitinib (JAVELIN 101)
- Pembrolizumab + Axitinib (KEYNOTE 426)
- Nivolumab + Cabozantinib (CHECKMATE 9ER)
- Pembrolizumab + Lenvatinib (CLEAR)

IO + VEGF

FIRST-LINE COMBINATIONS IN mRCC

- Ipilimumab + Nivolumab (CHECKMATE 214)

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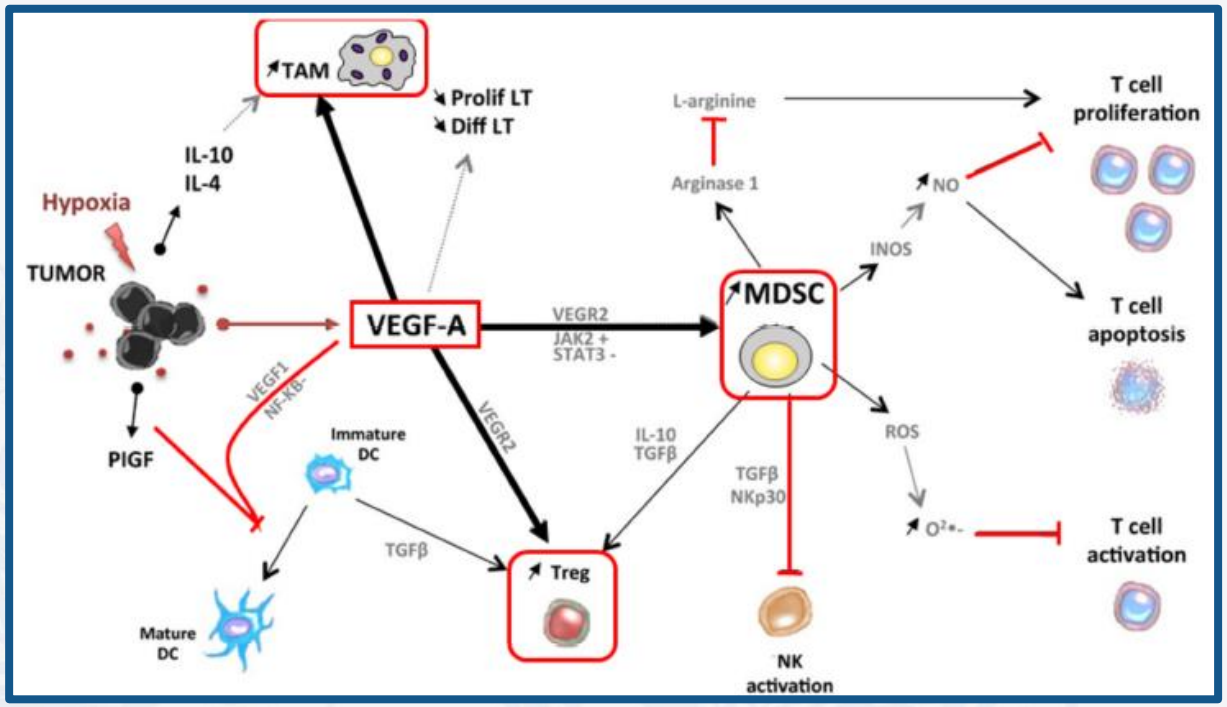
IO + VEGF

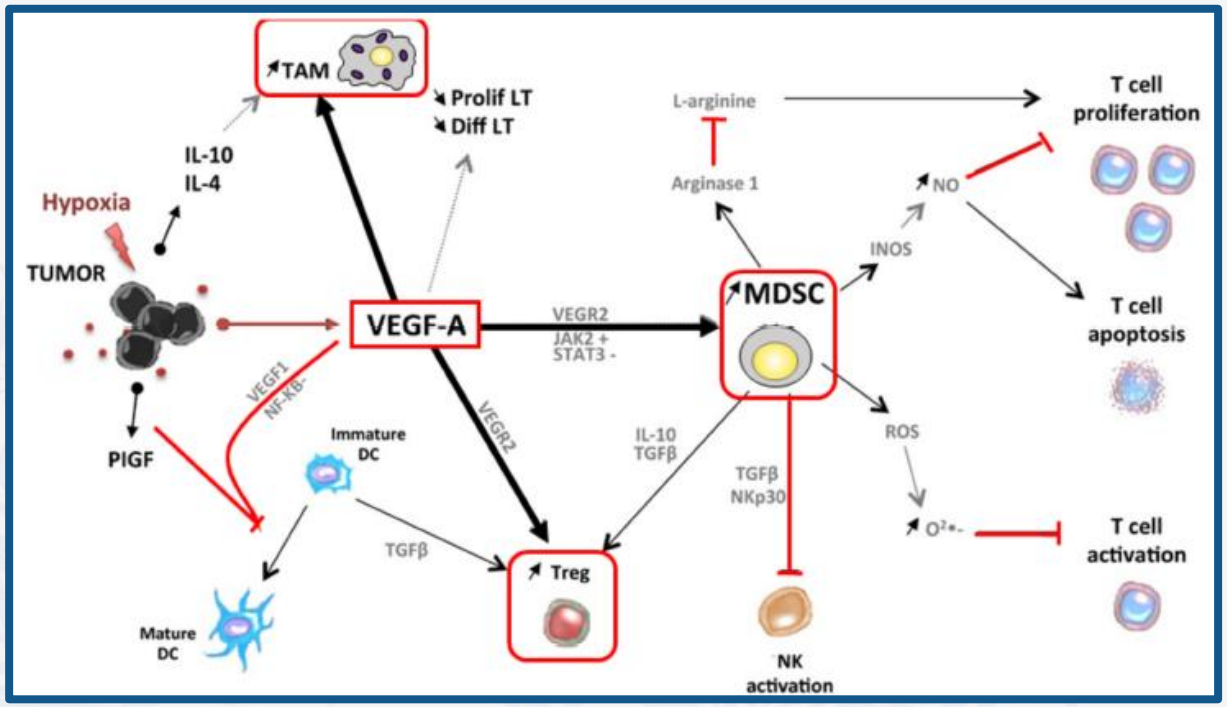
Rationale for Combined Immunotherapy with PD-1/PD-L1 Antibodies and VEGF Inhibitors



- VEGF enhances:
  - ✓ Mobilization and proliferation of various cells, including regulatory T cells (Tregs)
  - ✓ Release of immunosuppressive cytokines
  - ✓ Mobilization of tumor-associated macrophages (TAMs)
- Tregs and TAMs promote tumor growth through the release of VEGF and angiopoietin-2

Kudo M, Cancers 2020

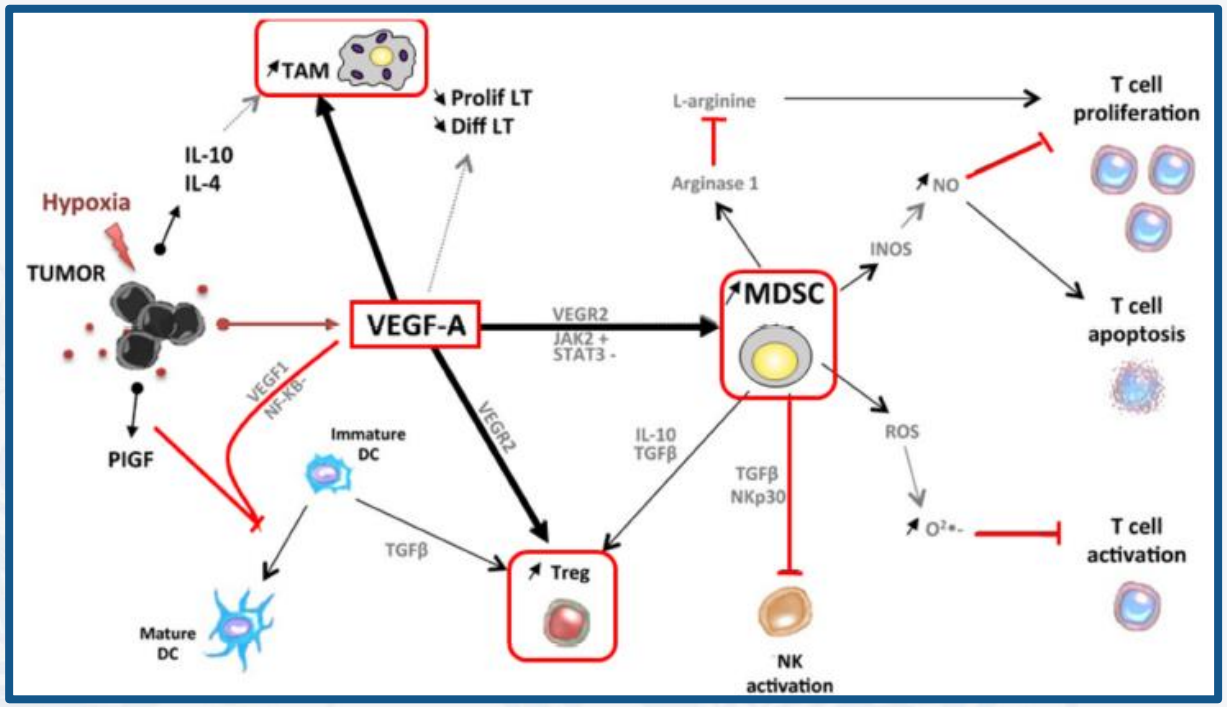
Rationale for Combined Immunotherapy with PD-1/PD-L1 Antibodies and VEGF Inhibitors



- Activate myeloid-derived suppressor cells (MDSCs), which in turn release more VEGF
- Inhibits dendritic cell maturation and antigen presentation in the priming phase.
- Reduces the proliferation and activation of naive CD8+ cells by suppressing dendritic cell activity even in the presence of neoantigens
- Prevents antigen-activated CD8+ cells from infiltrating the tumor tissue through its effects on tumor angiogenesis

Kudo M, Cancers 2020

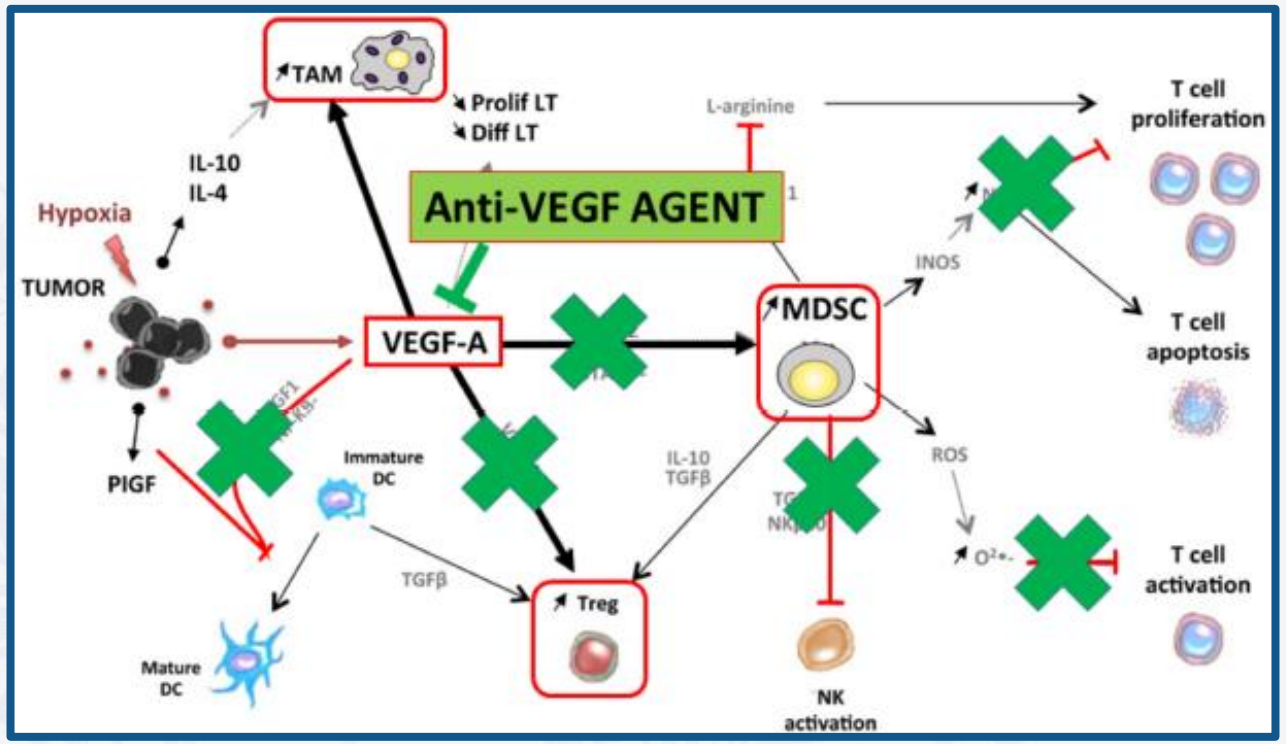
Rationale for Combined Immunotherapy with PD-1/PD-L1 Antibodies and VEGF Inhibitors



VEGF PROMOTES IMMUNE ESCAPE AT ALMOST EVERY STEP OF THE CANCER IMMUNITY CYCLE

Kudo M, Cancers 2020

Rationale for Combined Immunotherapy with PD-1/PD-L1 Antibodies and VEGF Inhibitors

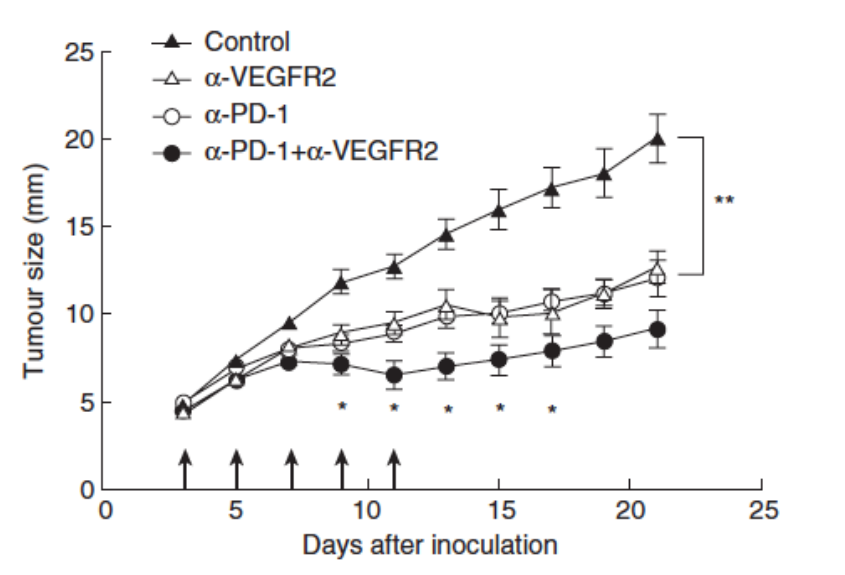


- VEGF inhibitors reprogram the immunosuppressive tumor microenvironment into an immunostimulatory environment
- The administration of PD-1/ PD-L1 antibodies under such conditions enhances the antitumor activity of T cells

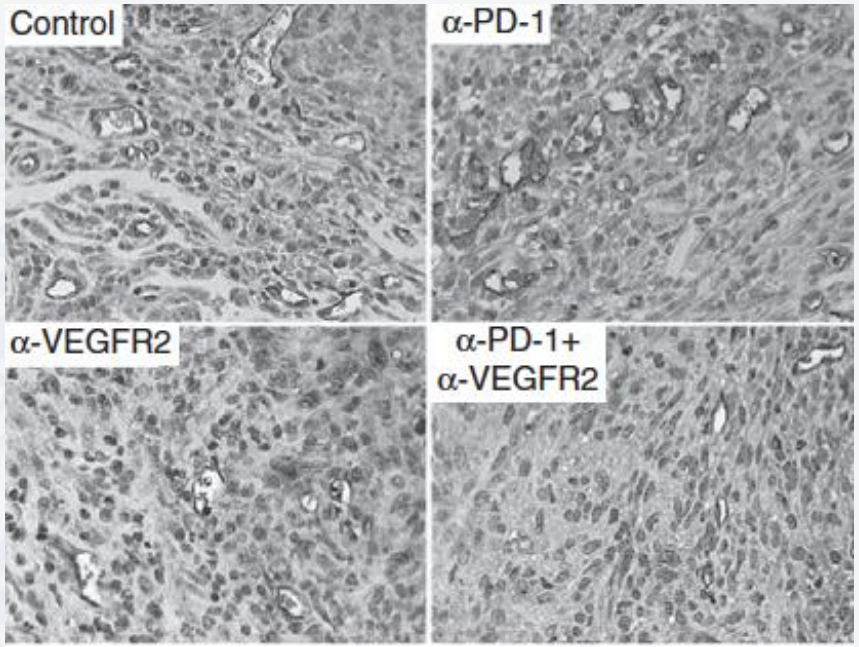
Kudo M, Cancers 2020

Rationale for Combined Immunotherapy with PD-1/PD-L1 Antibodies and VEGF Inhibitors

Simultaneous blockade of PD-1 and VEGFR2 induced synergistic anti-tumour effect in vivo



Treatment with VEGFR2 monoclonal antibody (mAb) and anti-PD-1 inhibited tumour neovascularization.



Yasuda S et al. Clinical and Experimental Immunology 2013

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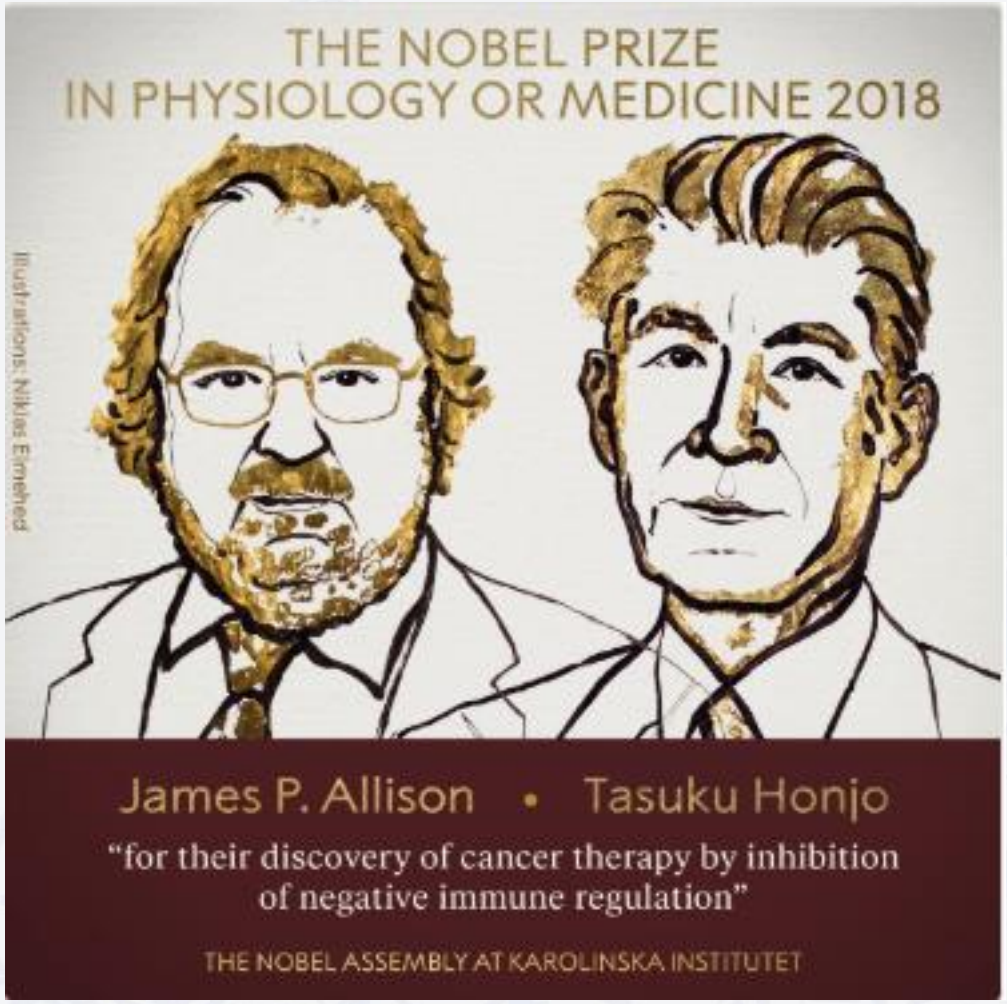
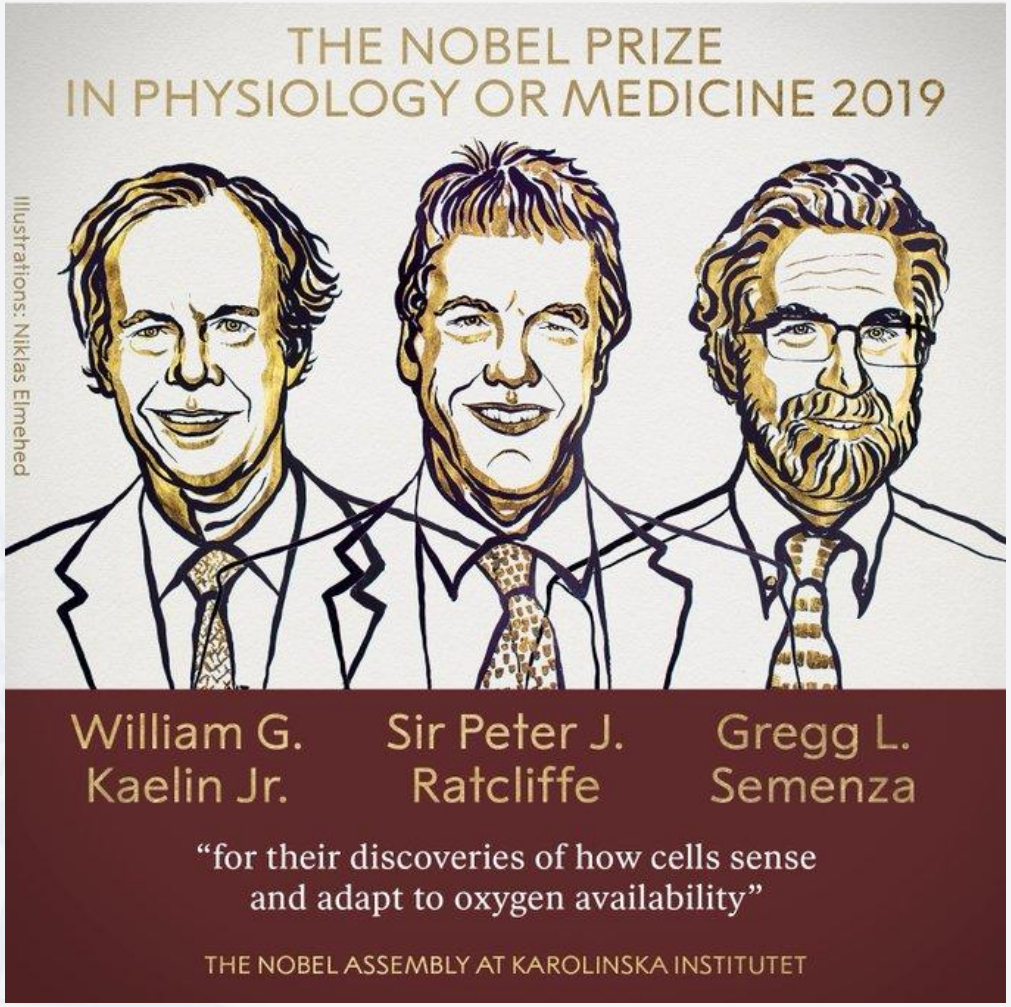
2018-2019 NOBEL PRIZES IN MEDICINE





IO + ANTI-VEGF COMBINATIONS: PHASE I TRIALS

	Nivolumab Sunitinib	Nivolumab Pazopanib	Pembrolizumab Pazopanib	Avelumab Axitinib	Pembrolizumab Axitinib	Nivolumab Cabozantinib	Pembrolizumab Lenvatinib
n	33	20	41	55	52	23	30
RG (%)	54.5	45	----------	58	73	53.9	66.7
RC (%)	6.1	0	----------	3	8	0	0
RP (%)	48.5	45	----------	55	65	53.9	69

Amin A, et al. IKCS2017.
Choueiri TK MB, et al. J Clin Oncol 35,2017 (suppl;4504).
Choueiri TK, et al. Lancet Oncol 2018;19(4): 451.
Atkins B, et al. Lancet Oncol 2018;19(3):405.
Nadal R, et al. J Clin Oncol 2018;36(suppl;abstr4528).
Chung-Han L, et al. J Clin Oncol 2018;36(suppl;abstr4560.

IO + ANTI-VEGF COMBINATIONS: PHASE III TRIALS

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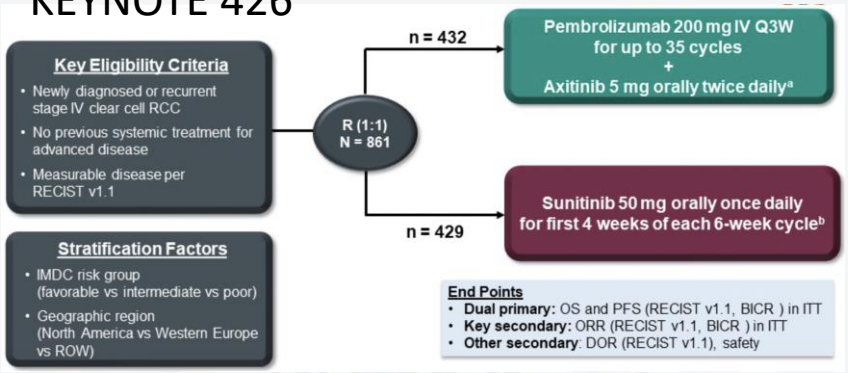
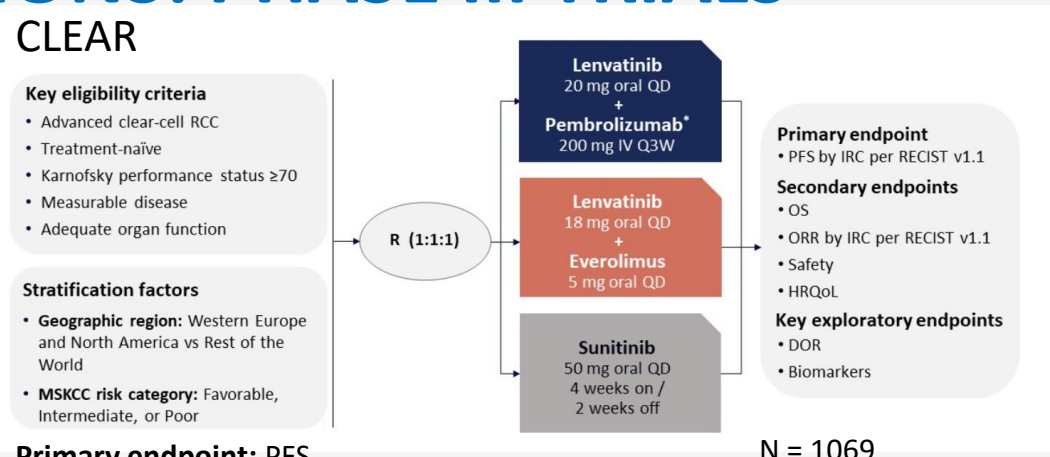
KEYNOTE 426



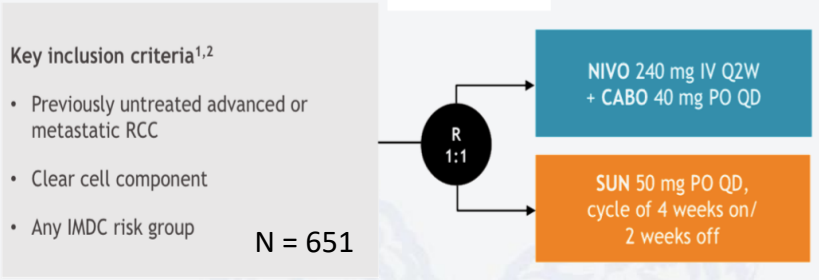
CLEAR



Primary endpoint: PFS

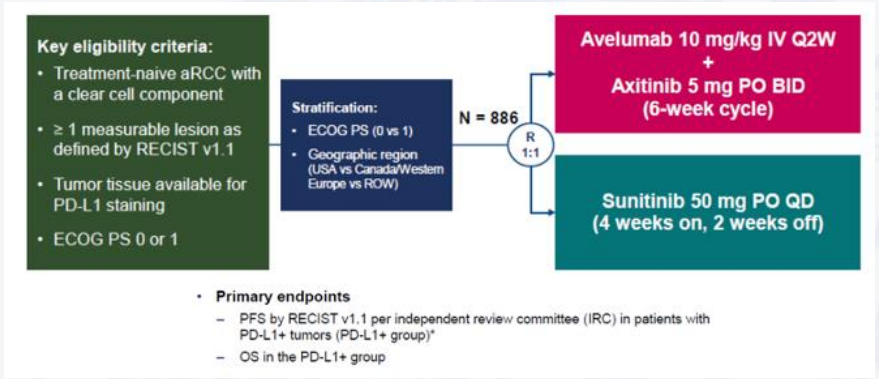
N = 1069

CHECKMATE 9ER

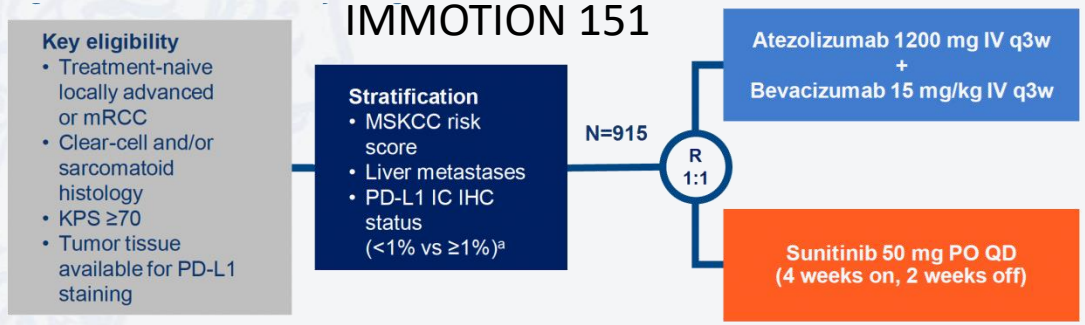


Primary endpoint: PFS

JAVELIN RENAL 101



IMMOTION 151



Co-primary endpoints
- PFS by INV assessment in PD-L1+
- OS in ITT

Other endpoints
- OS in PD-L1+
- Safety
- Exploratory biomarkers

Rini BI, et al. N Engl J Med 2019 Mar 21;380(12):1116-1127. Motzer R, et al. N Engl J Med 2019 Mar 21;380(12):1103-1115.
Rini BI, et al. Lancet 2019 Jun 15;393(10189):2404-2415. Choueiri TK, et al. N Engl J Med 2021;384:829-41. Motzer R, et al. N Engl J Med 2021;384:1289-300.

IO+VEGF COMBINATIONS IN FIRST-LINE RCC THERAPY

- Atezolizumab+Bevacizumab (IMMOTION 151)
- Pembrolizumab+Axitinib (KEYNOTE-426)
- Avelumab+Axitinib (JAVELIN 101)
- Nivolumab+Cabozantinib (CHECKMATE-9ER)
- Lenvatinib+Pembrolizumab (CLEAR)

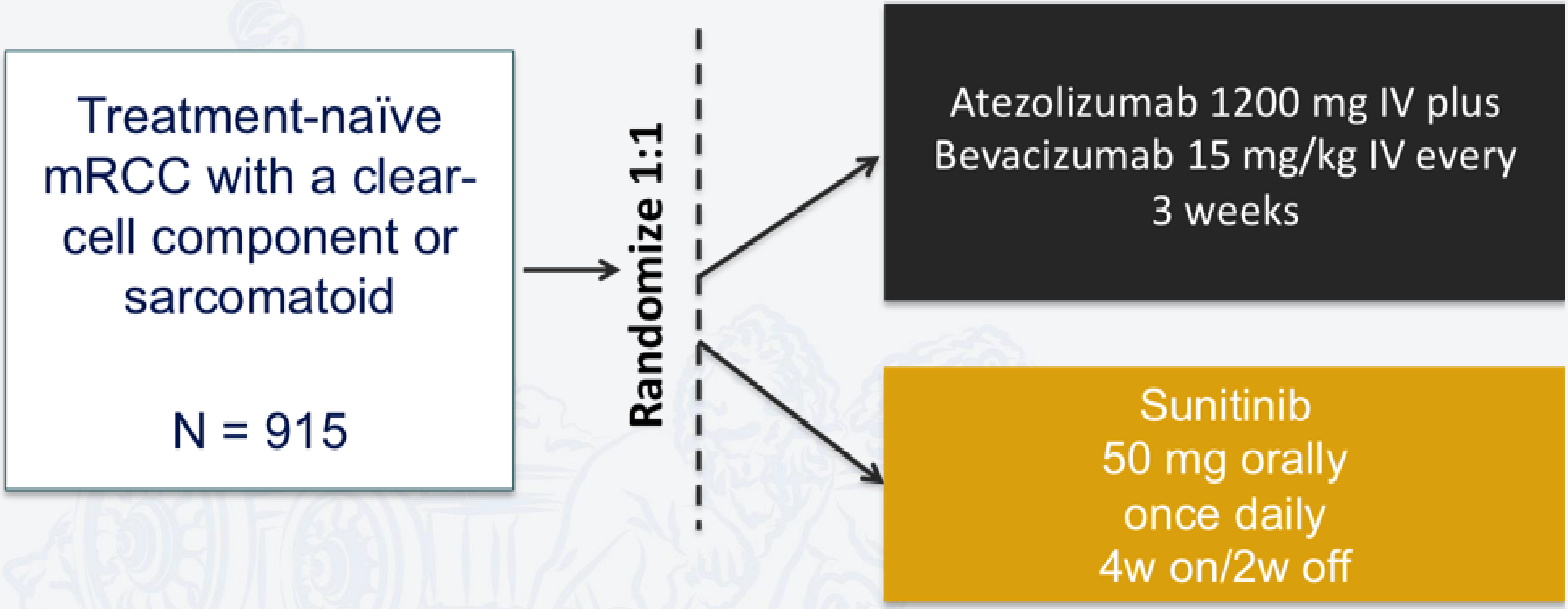
IO+VEGF COMBINATIONS IN FIRST-LINE RCC THERAPY

- **Atezolizumab+Bevacizumab (IMMOTION 151)**
- Pembrolizumab+Axitinib (KEYNOTE-426)
- Avelumab+Axitinib (JAVELIN 101)
- Nivolumab+Cabozantinib (CHECKMATE-9ER)
- Lenvatinib+Pembrolizumab (CLEAR)

Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial

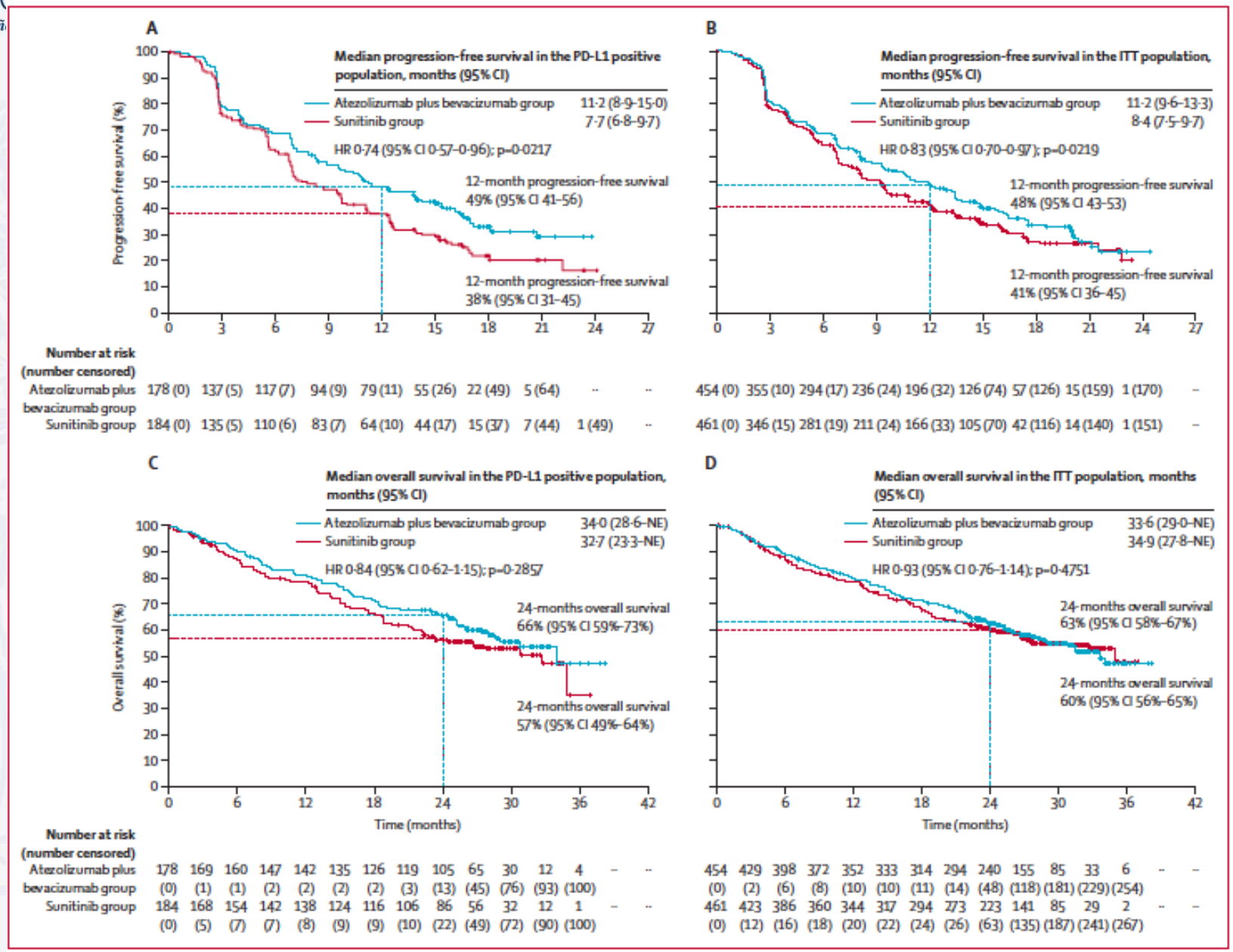
Brian I Rini, Thomas Powles, Michael B Atkins, Bernard Escudier, David F McDermott, Cristina Suarez, Sergio Bracarda, Walter M Stadler, Frede Donskov, Jae Lyun Lee, Robert Hawkins, Alain Ravaud, Boris Alekseev, Michael Staehler, Motohide Uemura, Ugo De Giorgi, Begoña Mellado, Camillo Porta, Bohuslav Melichar, Howard Gurney, Jens Bedke, Toni K Choueiri, Francis Parnis, Tarik Khaznadar, Alpa Thobhani, Shi Li, Elisabeth Piault-Louis, Gretchen Frantz, Mahrukh Huseni, Christina Schiff, Marjorie C Green, Robert J Motzer, on behalf of the IMmotion151 Study Group*

IMMOTION 151: STUDY DESIGN



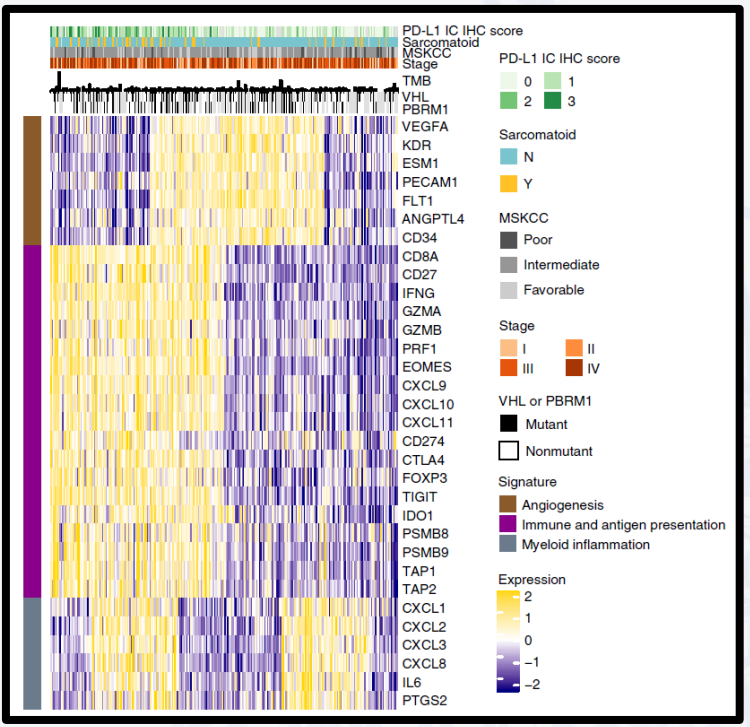
Co-primary endpoint: PFS in PD-L1+, OS in ITT

IMMOTION 151: OS AND PFS



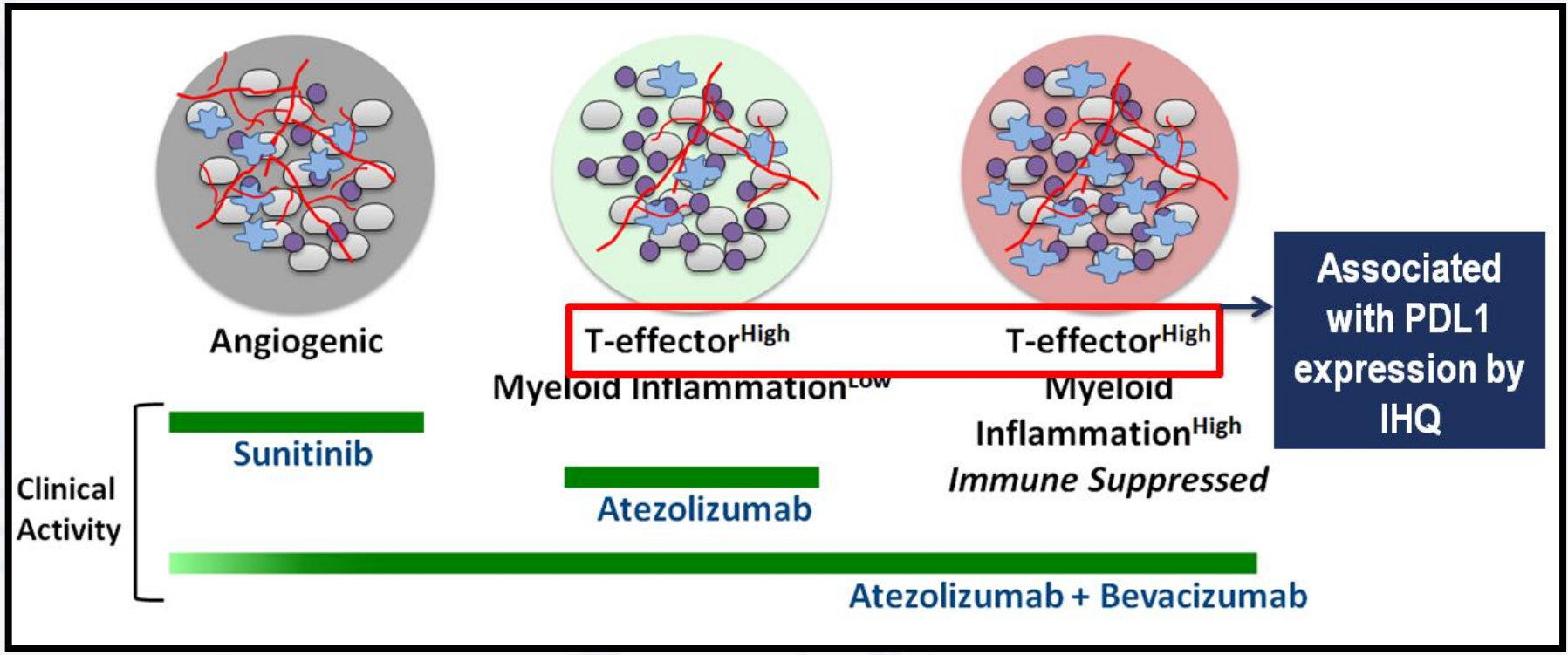
BIOMARKERS

IMMOTION 150: Gene Expression Profile



Biological subgroups based on relative gene expression levels of:

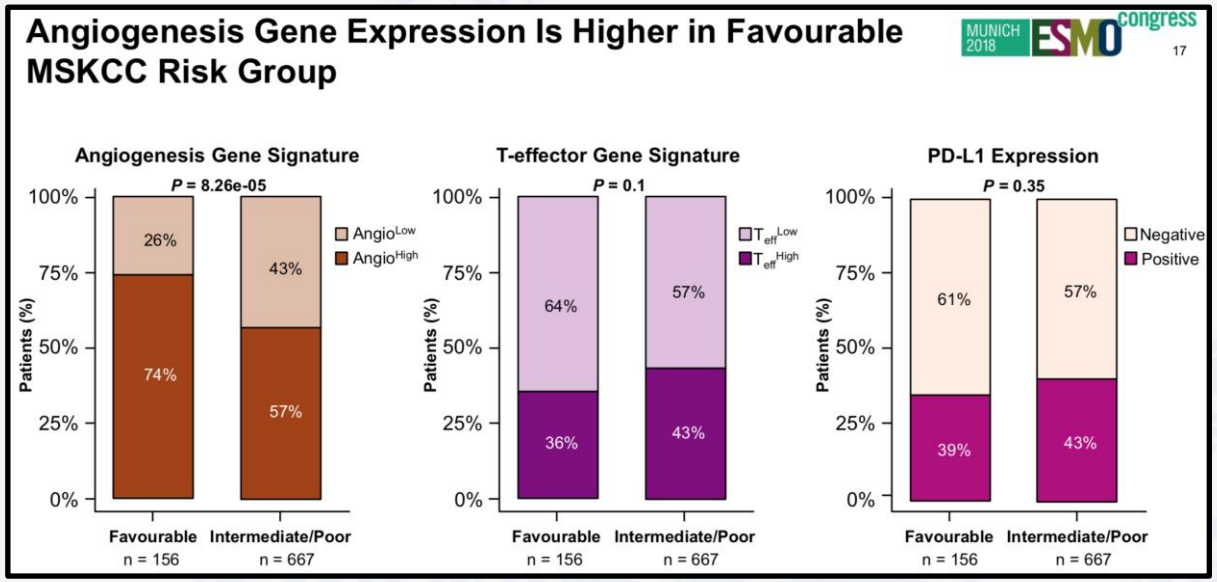
- Angiogenesis
- Immune and antigen presentation
- Myeloid inflammation

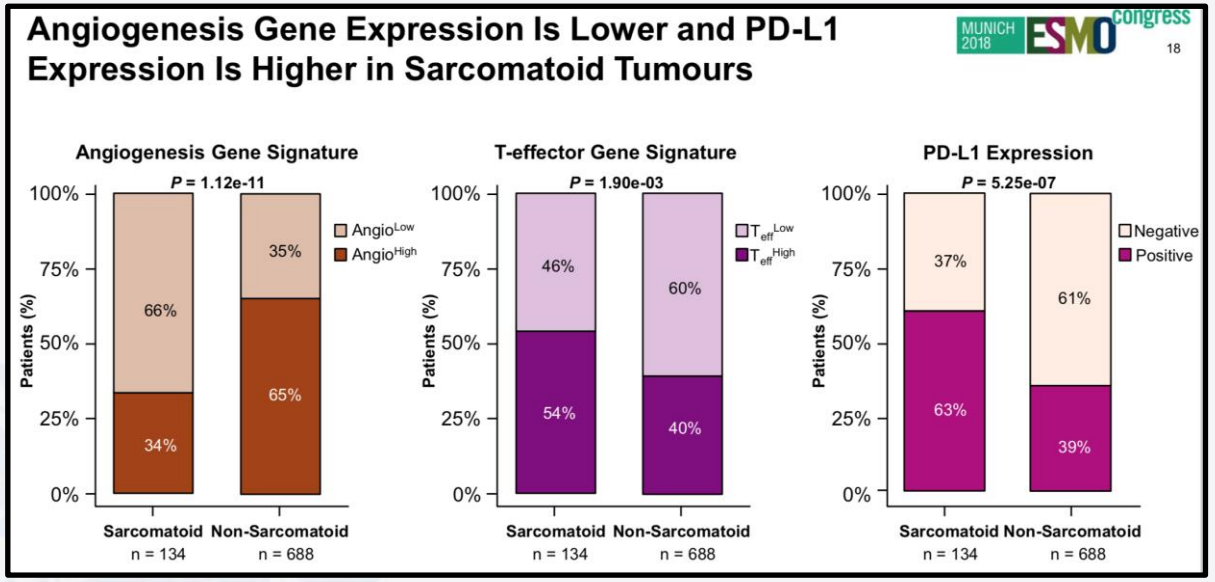


McDermott D, et al. IMmotion150 biomarkers: AACR 2017

BIOMARKERS

IMMOTION 151: Gene Expression Profile



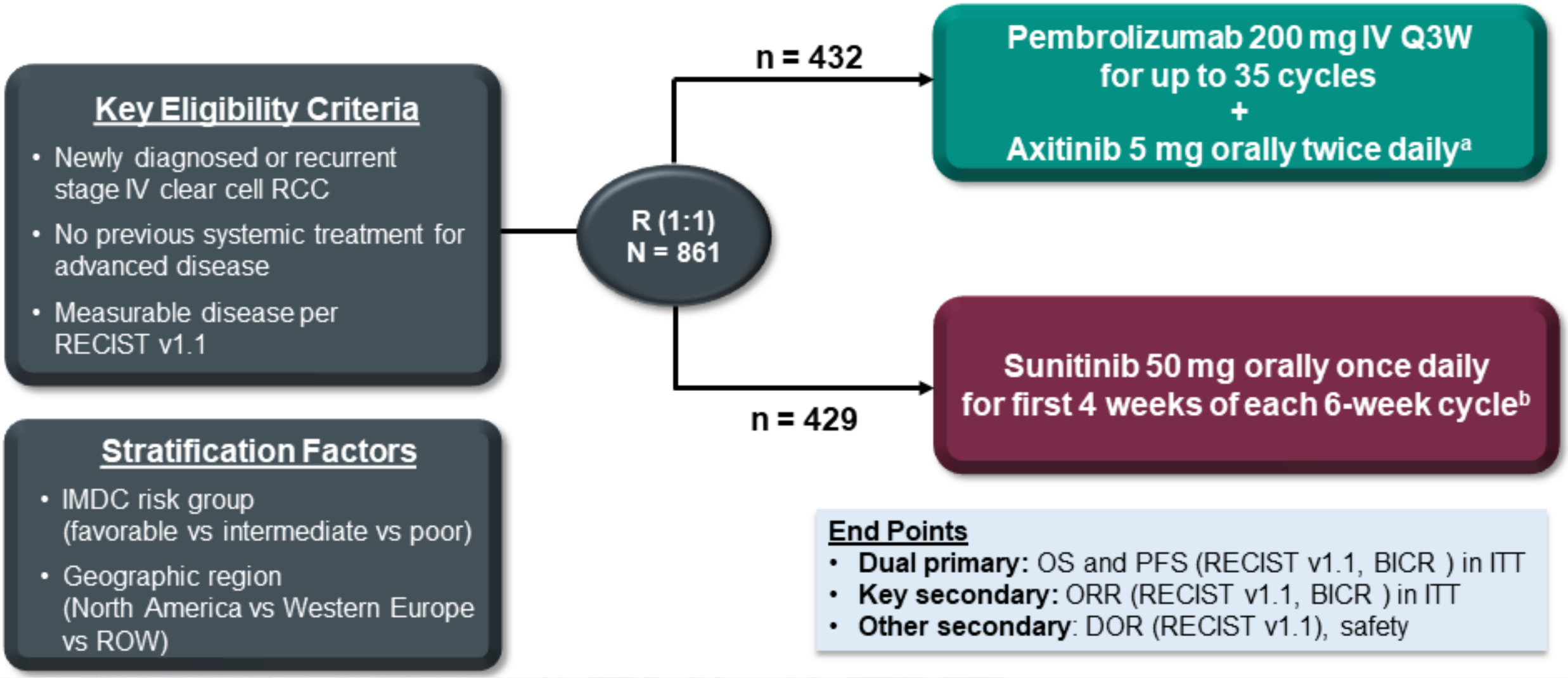


Rini B, ESMO 2018

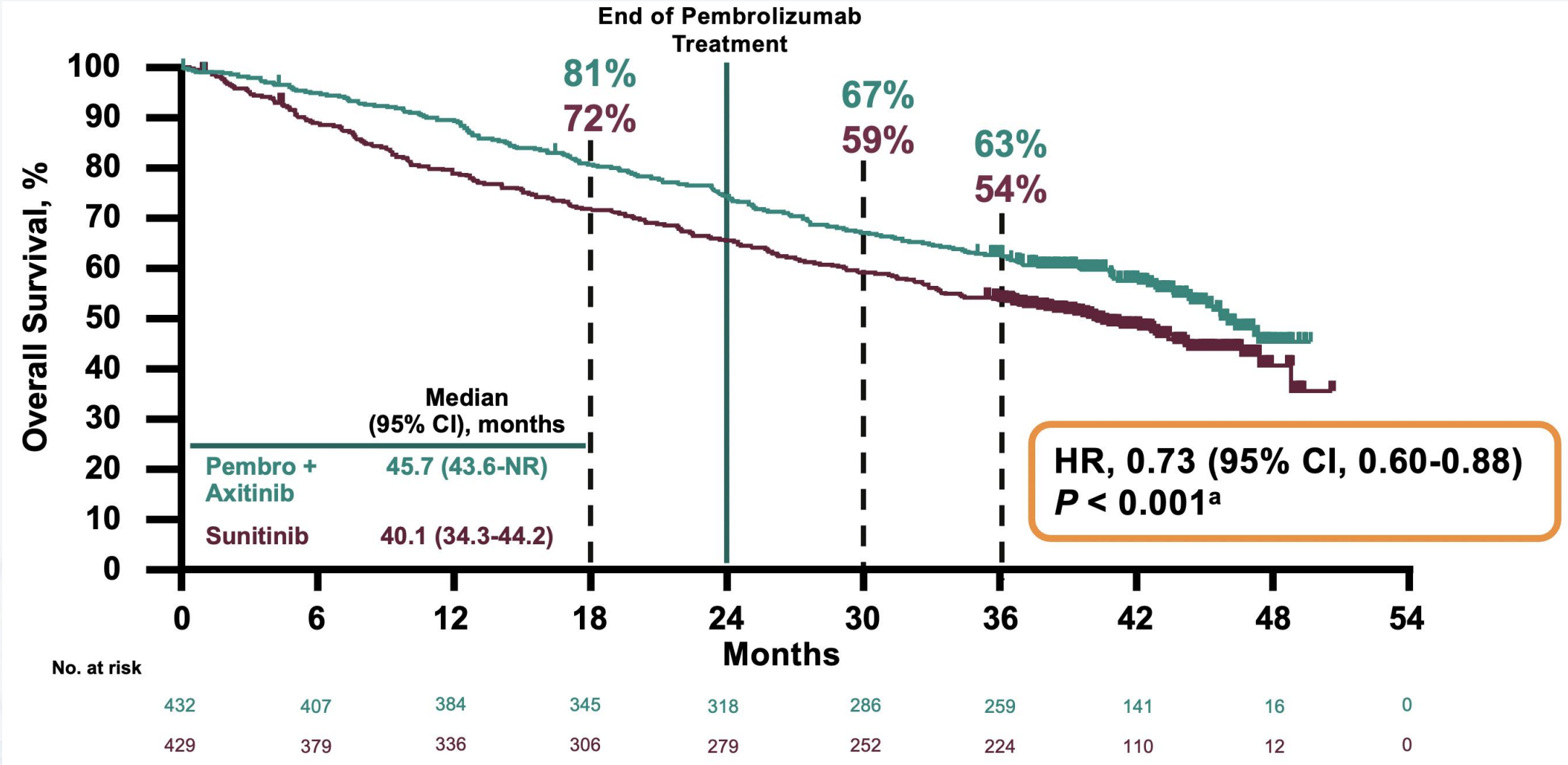
IO+VEGF COMBINATIONS IN FIRST-LINE RCC THERAPY

- ❑ Atezolizumab+Bevacizumab (IMMOTION 151)
- ❑ **Pembrolizumab+Axitinib (KEYNOTE-426)**
- ❑ Avelumab+Axitinib (JAVELIN 101)
- ❑ Nivolumab+Cabozantinib (CHECKMATE-9ER)
- ❑ Lenvatinib+Pembrolizumab (CLEAR)

KEYNOTE-426: STUDY DESIGN

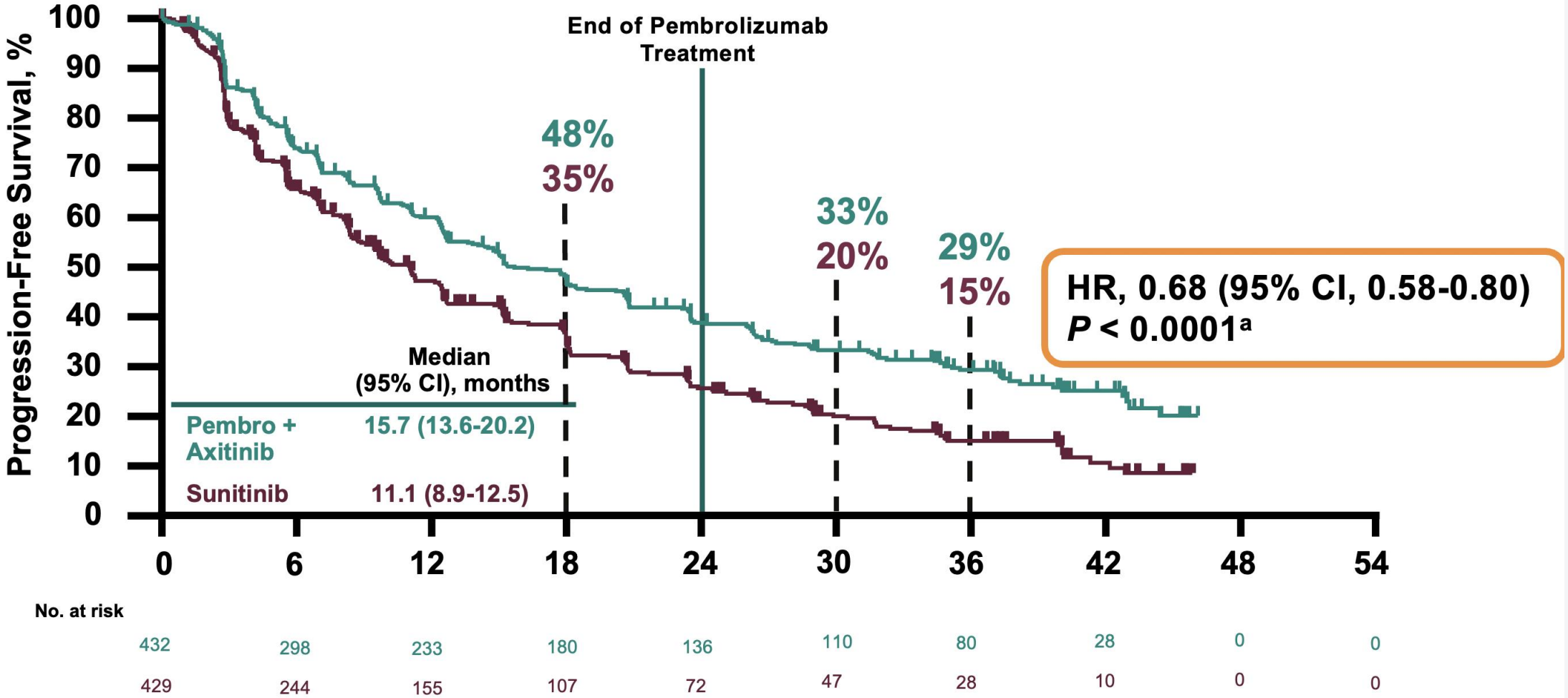


KEYNOTE-426: OS ITT POPULATION



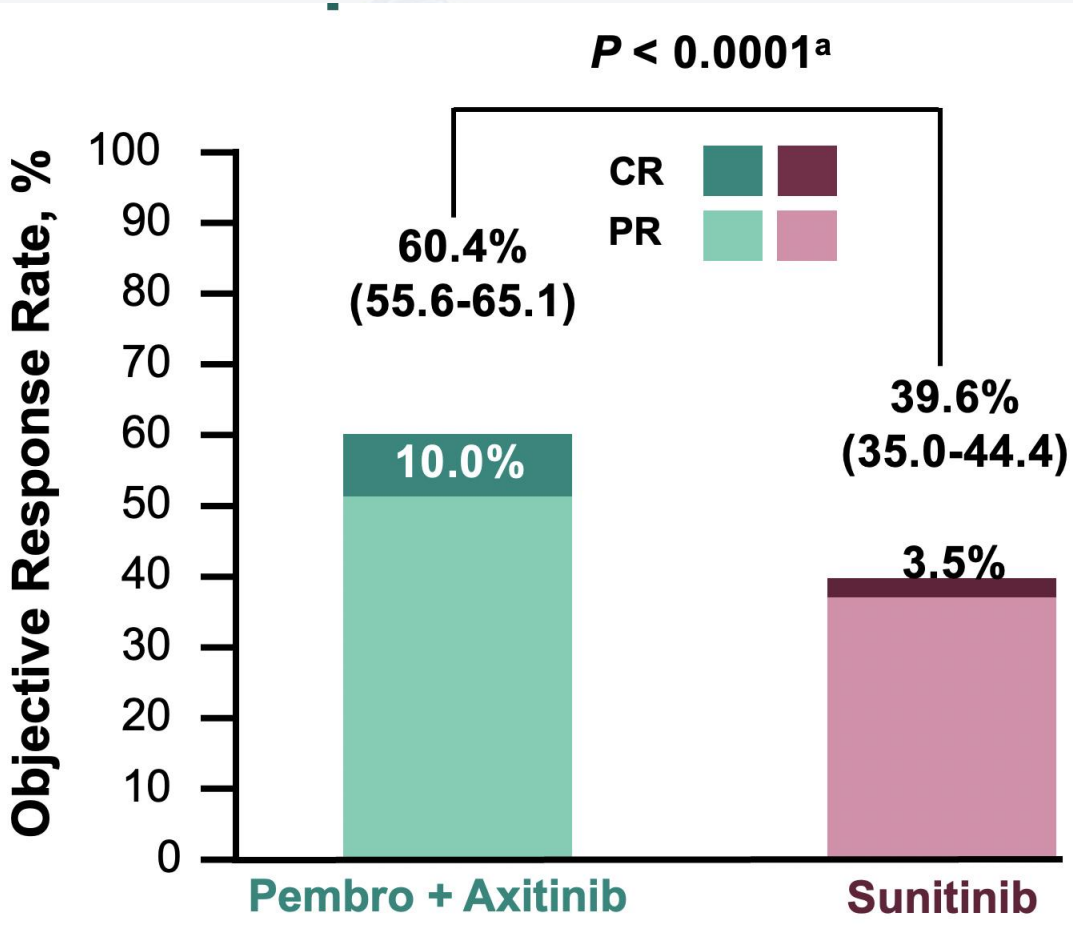
Rini BI, ASCO 2021

KEYNOTE-426: PFS ITT POPULATION



Rini BI, ASCO 2021

KEYNOTE-426: ORR



	Pembro + Axitinib n = 432	Sunitinib n = 429
Best response, n (%)		
CR	43 (10.0)	15 (3.5)
PR	218 (50.5)	155 (36.1)
SD	99 (22.9)	152 (35.4)
PD	49 (11.3)	73 (17.0)
NE[b]	7 (1.6)	6 (1.4)
NA[c]	16 (3.7)	28 (6.5)

Rini BI, ASCO 2021

IO+VEGF COMBINATIONS IN FIRST-LINE RCC THERAPY

- ❑ Atezolizumab+Bevacizumab (IMMOTION 151)
- ❑ Pembrolizumab+Axitinib (KEYNOTE-426)
- ❑ **Avelumab+Axitinib (JAVELIN 101)**
- ❑ Nivolumab+Cabozantinib (CHECKMATE-9ER)
- ❑ Lenvatinib+Pembrolizumab (CLEAR)

JAVELIN 101: STUDY DESIGN

Key eligibility criteria:

- Treatment-naive 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

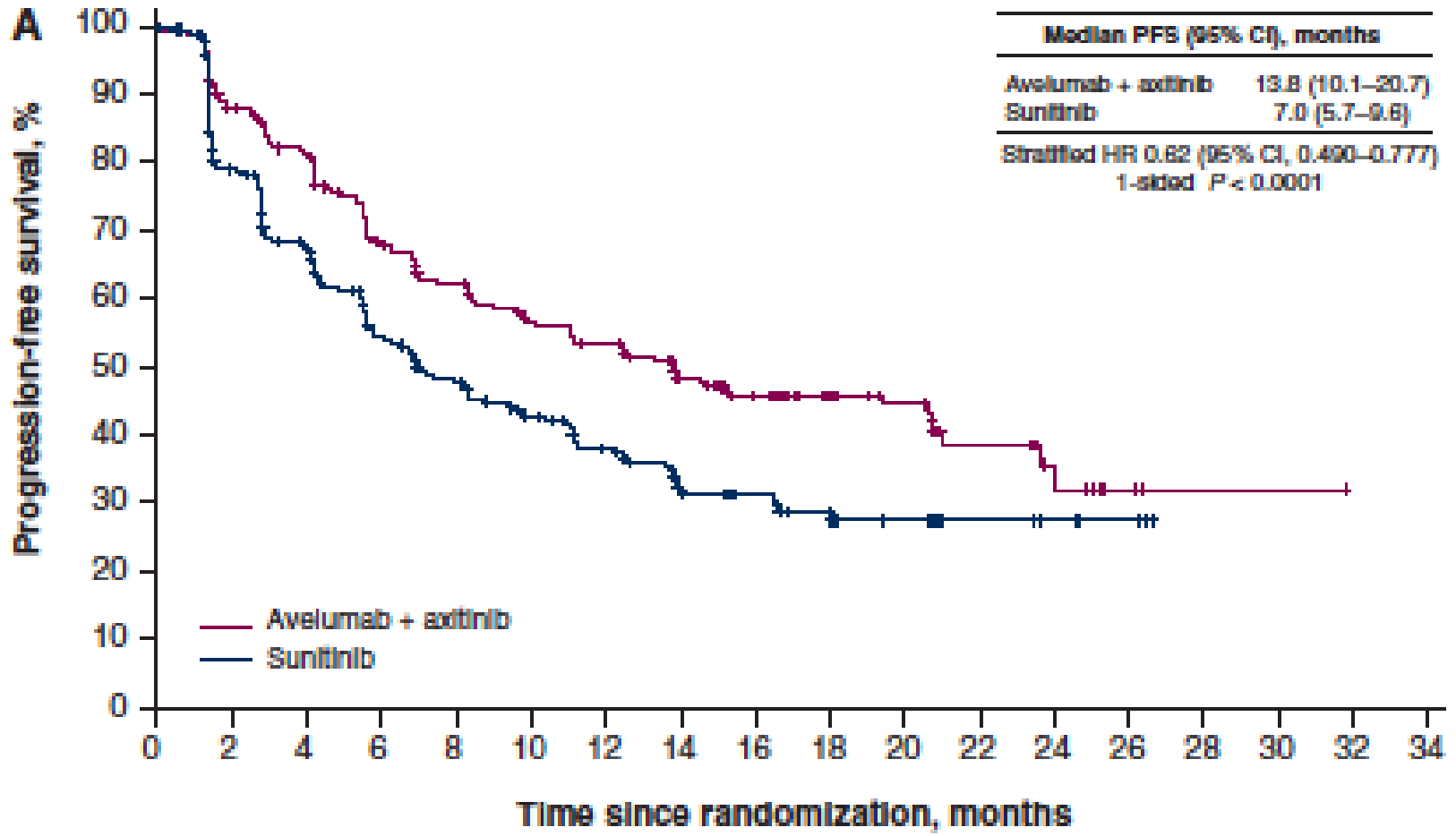
R 1:1

Avelumab 10 mg/kg IV Q2W + Axitinib 5 mg PO BID (6-week cycle)

Sunitinib 50 mg PO QD (4 weeks on, 2 weeks off)

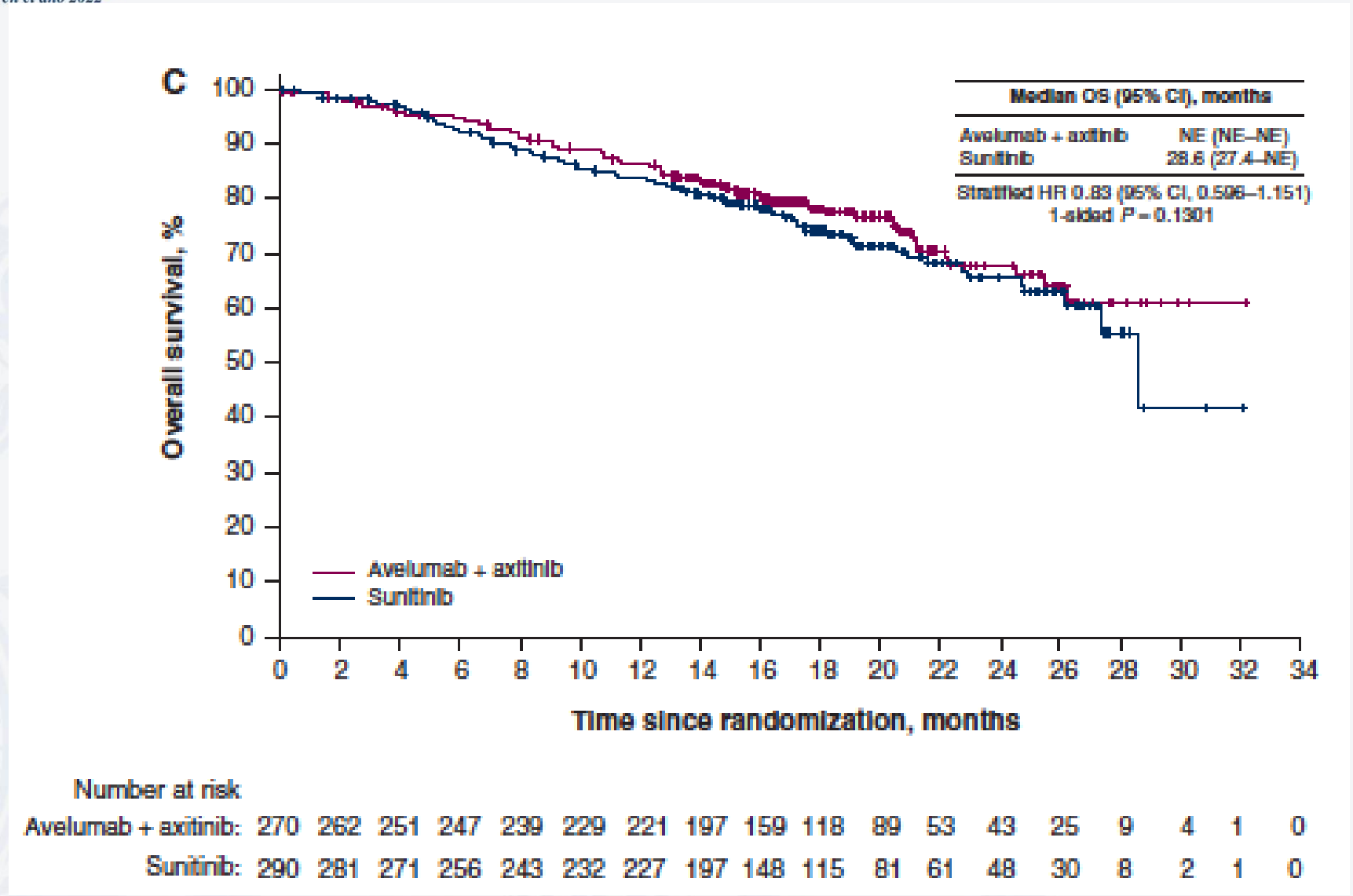
- **Primary endpoints**
  - PFS by RECIST v1.1 per independent review committee (IRC) in patients with PD-L1+ tumors (PD-L1+ group)*
  - OS in the PD-L1+ group
- **Key secondary endpoints**
  - PFS per IRC in the overall population
  - OS in the overall population

JAVELIN 101: PFS in PD-L1+



Choueiri TK, Annals of Oncology 2020

JAVELIN 101: OS in PDL1+



Choueiri TK, Annals of Oncology 2020

JAVELIN 101: ORR

Secondary endpoint

Confirmed objective response

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

IO+VEGF COMBINATIONS IN FIRST-LINE RCC THERAPY

- ❑ Atezolizumab+Bevacizumab (IMMOTION 151)
- ❑ Pembrolizumab+Axitinib (KEYNOTE-426)
- ❑ Avelumab+Axitinib (JAVELIN 101)
- ❑ **Nivolumab+Cabozantinib (CHECKMATE-9ER)**
- ❑ Lenvatinib+Pembrolizumab (CLEAR)

CHECKMATE 9ER: STUDY DESIGN

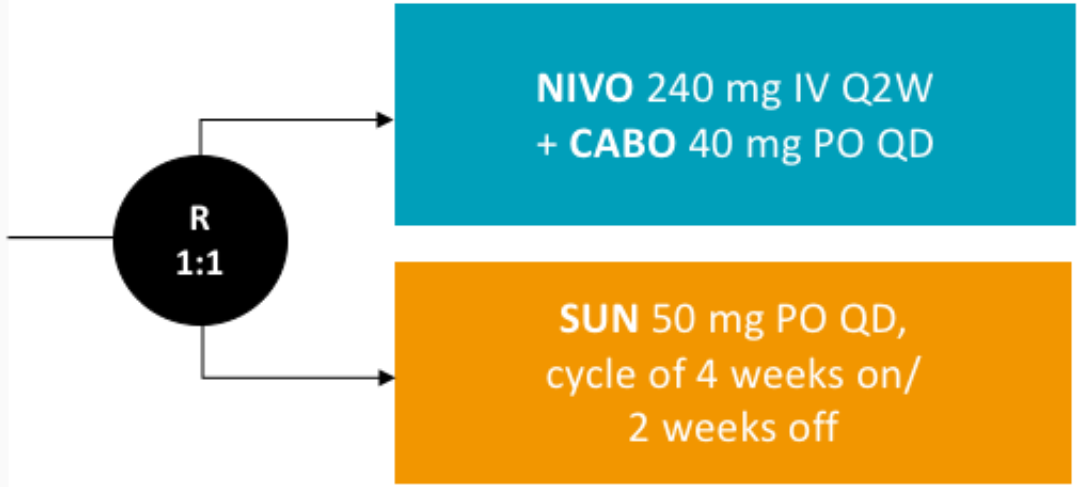
N = 651

Key inclusion criteria[1,2]

- Previously untreated advanced or metastatic RCC with a clear cell component
- Any IMDC risk group
- No prior systemic therapy

Stratification factors:

- IMDC risk score
- Tumor PD-L1 expression[a]
- Geographic region



Treat until RECIST v1.1–defined progression or unacceptable toxicity[b]

Median study follow-up, 18.1 months (range, 10.6–30.6 months)

Primary endpoint: PFS per BICR using RECIST v1.1

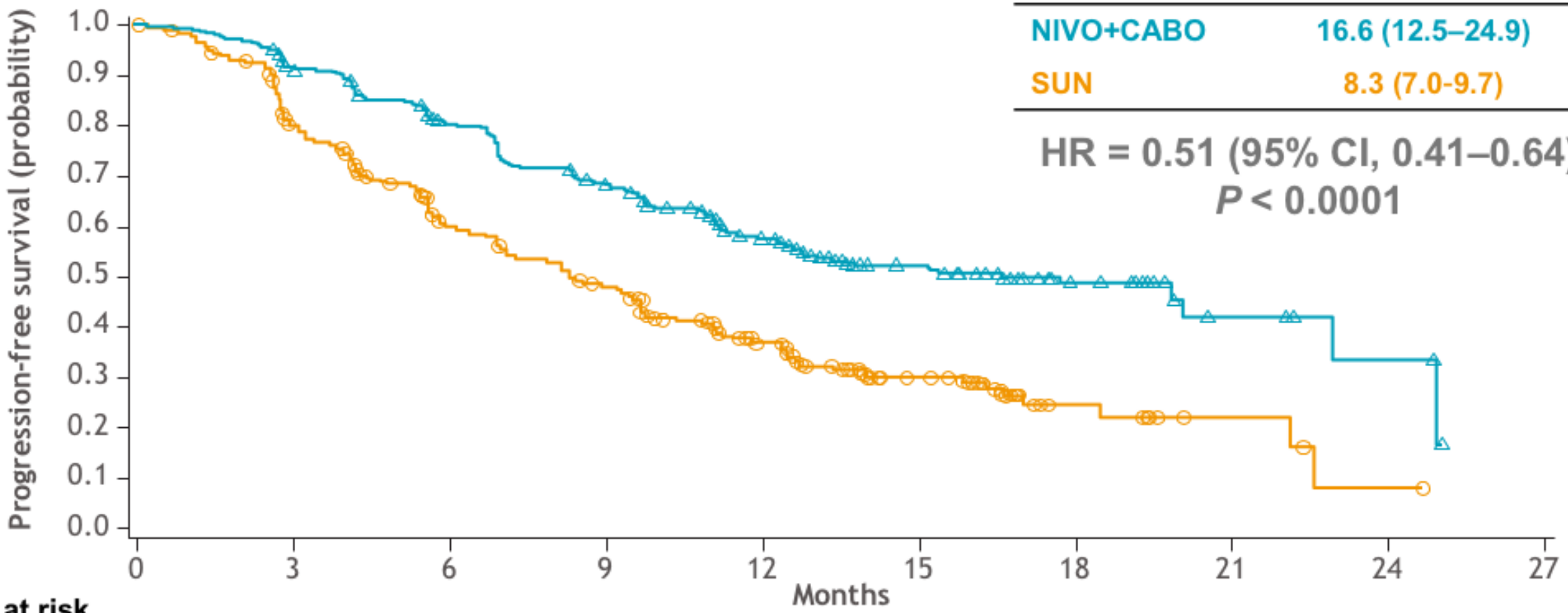
Secondary endpoints: OS, ORR per BICR using RECIST v1.1, and safety

Choueiri T, ESMO 2020

CHECKMATE 9ER: PFS

Median PFS, months (95% CI)	
NIVO+CABO	16.6 (12.5–24.9)
SUN	8.3 (7.0-9.7)

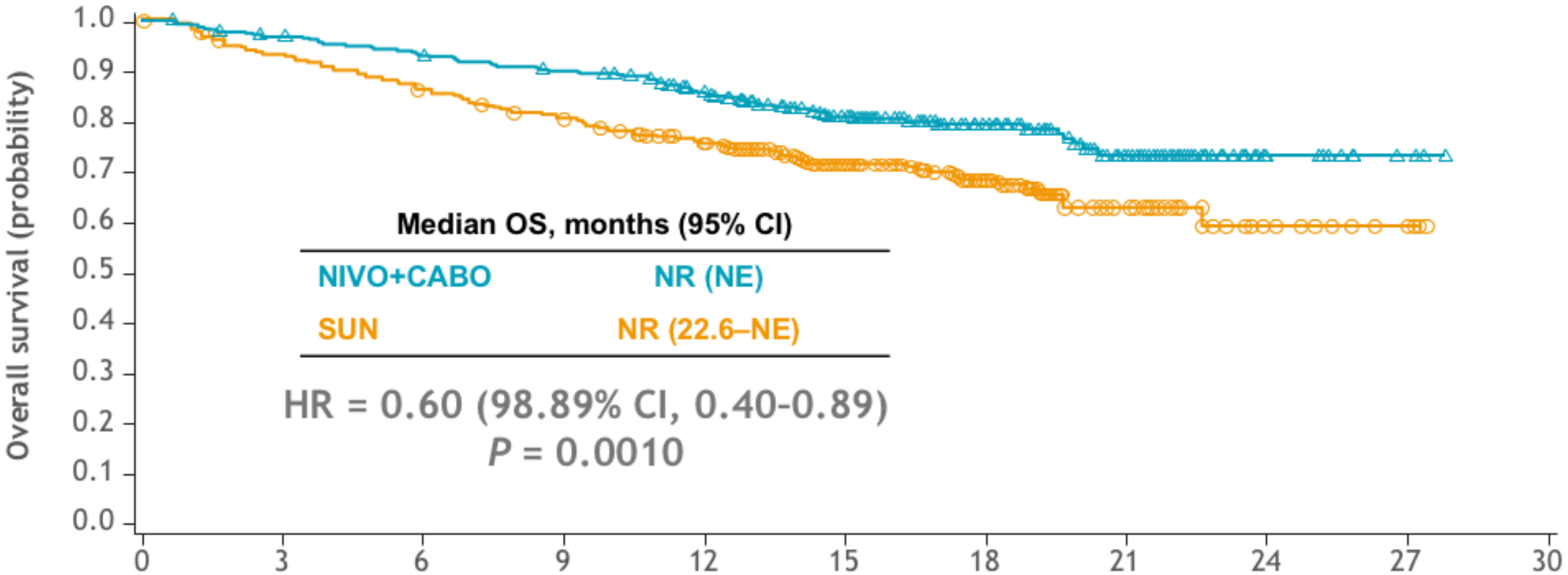
HR = 0.51 (95% CI, 0.41–0.64)
P < 0.0001



No. at risk									
NIVO+CABO	323	279	234	196	144	77	35	11	4	0
SUN	328	228	159	122	79	31	10	4	1	0

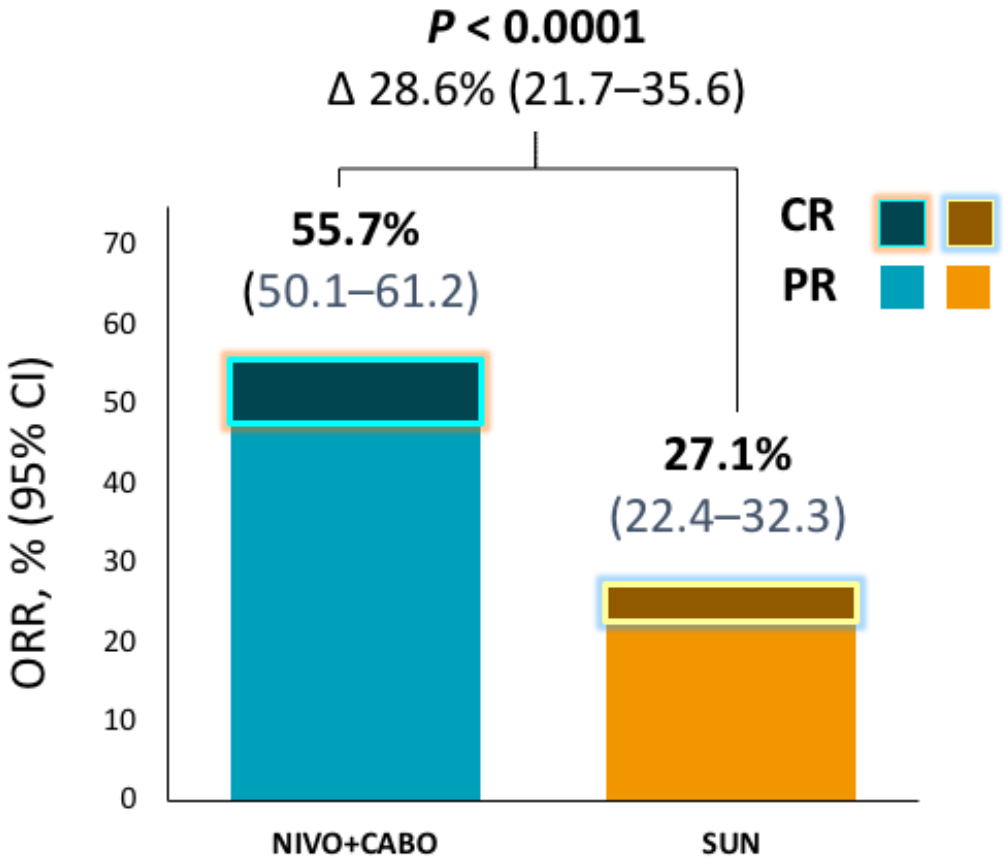
Choueiri T, ESMO 2020

CHECKMATE 9ER: OS



Choueiri T, ESMO 2020

CHECKMATE 9ER: ORR



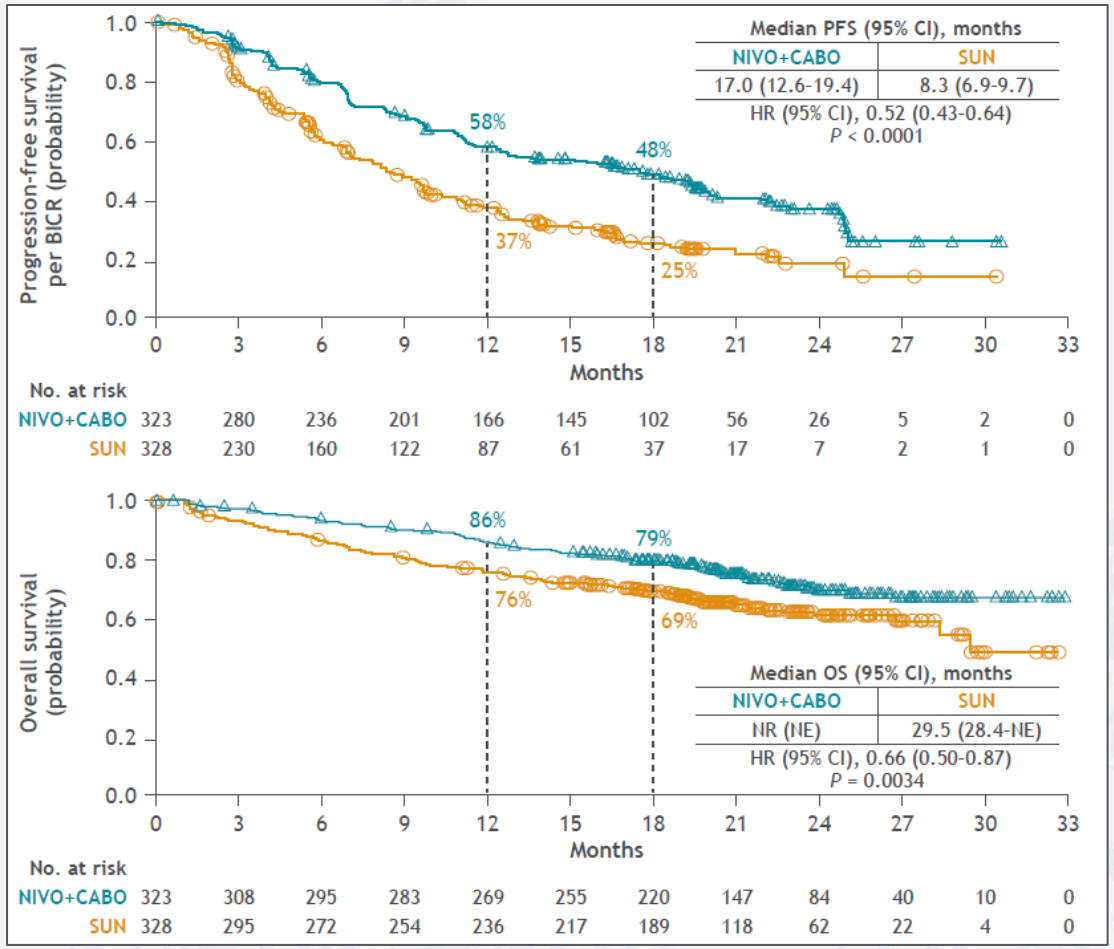
Outcome, %	NIVO+CABO (N = 323)	SUN (N = 328)
Complete response	8.0	4.6
Partial response	47.7	22.6
Stable disease	32.2	42.1
Progressive disease	5.6	13.7
Not evaluable/not assessed[a]	6.5	17.1
Median time to response (range), months[b]	2.8 (1.0–19.4)	4.2 (1.7–12.3)
Median duration of response (95% CI), months[b]	20.2 (17.3–NE)	11.5 (8.3–18.4)

- ORR favored NIVO+CABO over SUN across subgroups including by IMDC risk status, tumor PD-L1 expression (≥ 1% vs < 1%), and bone metastases

Choueiri T, ESMO 2020

EFFICACY OUTCOMES WITH EXTENDED FOLLOW-UP IN THE ITT POPULATION

PFS per BICR and OS in the ITT population



BICR-confirmed ORR per RECIST v1.1 in the ITT population

Outcome	NIVO+CABO (n = 323)	SUN (n = 328)
ORR (95% CI), %	54.8 (49.2–60.3)	28.4 (23.5–33.6)
Odds ratio estimate (95% CI)	3.2 (2.3–4.4)	
Best overall response, n (%)		
Complete response	30 (9.3)	14 (4.3)
Partial response	147 (45.5)	79 (24.1)
Stable disease	108 (33.4)	136 (41.5)
Progressive disease	20 (6.2)	45 (13.7)
UTD	18 (5.6)	53 (16.2)
Not reported	0	1 (0.3)
Median TTR (range), months	2.8 (1.0–11.0)	4.2 (1.7–20.2)
Median DOR (95% CI), months	21.7 (17.3–NE)	12.7 (9.6–20.7)
Probability of ongoing response at 18 months (95% CI), %	56 (46–64)	43 (30–55)

- At a median follow-up for OS of 23.5 (range, 16.0–36.0) months, NIVO+CABO continued to show superior PFS, OS, and ORR versus SUN
- Overall, 94% of patients experienced any reduction from baseline in sum of diameter of target lesions, and 71% had ≥ 30% reduction with NIVO+CABO; 85% of patients experienced any reduction, and 43% had ≥ 30% reduction with SUN

BICR, blinded independent central review; CABO, cabozantinib; DOR, duration of response; ITT, intent-to-treat; NE, not estimable; NIVO, nivolumab; NR, not reached; ORR, objective response rate, OS, overall survival; PFS, progression-free survival; SUN, sunitinib; TTR, time to response; UTD, unable to determine.

Motzer RJ, ASCO GU 2021

IO+VEGF COMBINATIONS IN FIRST-LINE RCC THERAPY

- ❑Atezolizumab+Bevacizumab (IMMOTION 151)
- ❑Pembrolizumab+Axitinib (KEYNOTE-426)
- ❑Avelumab+Axitinib (JAVELIN 101)
- ❑Nivolumab+Cabozantinib (CHECKMATE-9ER)
- ❑**Lenvatinib+Pembrolizumab (CLEAR)**

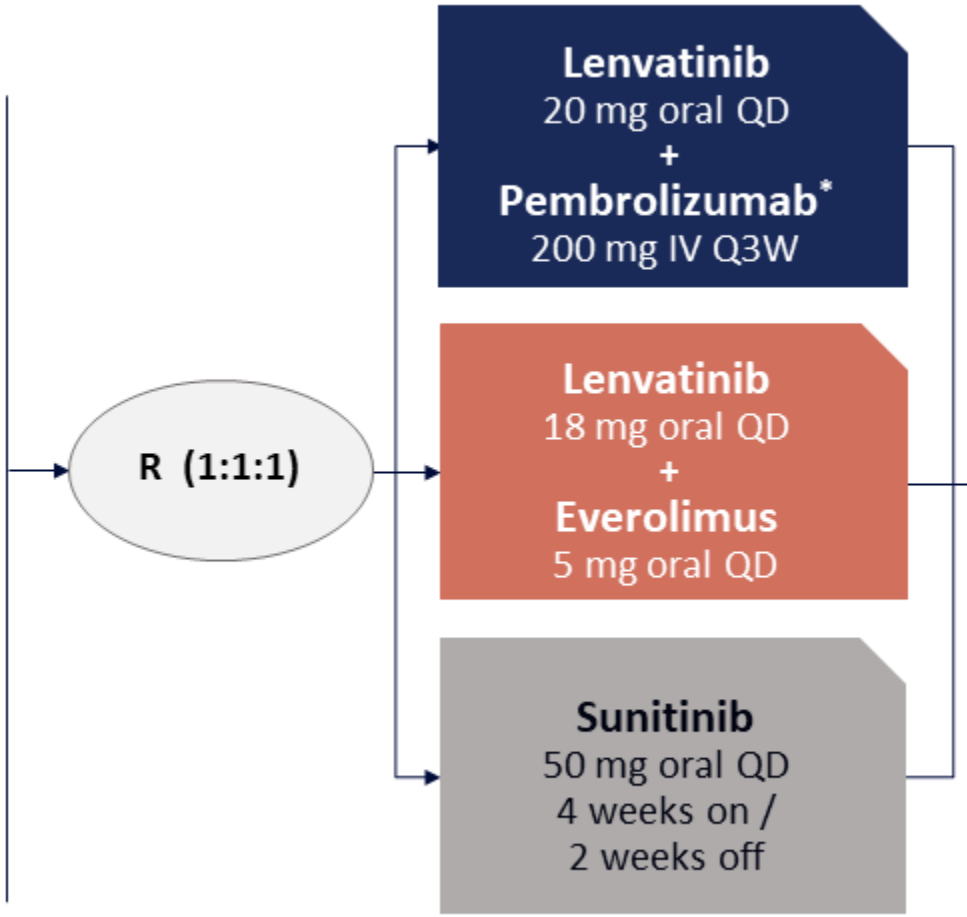
CLEAR: STUDY DESIGN

Key eligibility criteria

- Advanced clear-cell RCC
- Treatment-naïve
- Karnofsky performance status ≥70
- Measurable disease
- Adequate organ function

Stratification factors

- **Geographic region:** Western Europe and North America vs Rest of the World
- **MSKCC risk category:** Favorable, Intermediate, or Poor



Primary endpoint

- PFS by IRC per RECIST v1.1

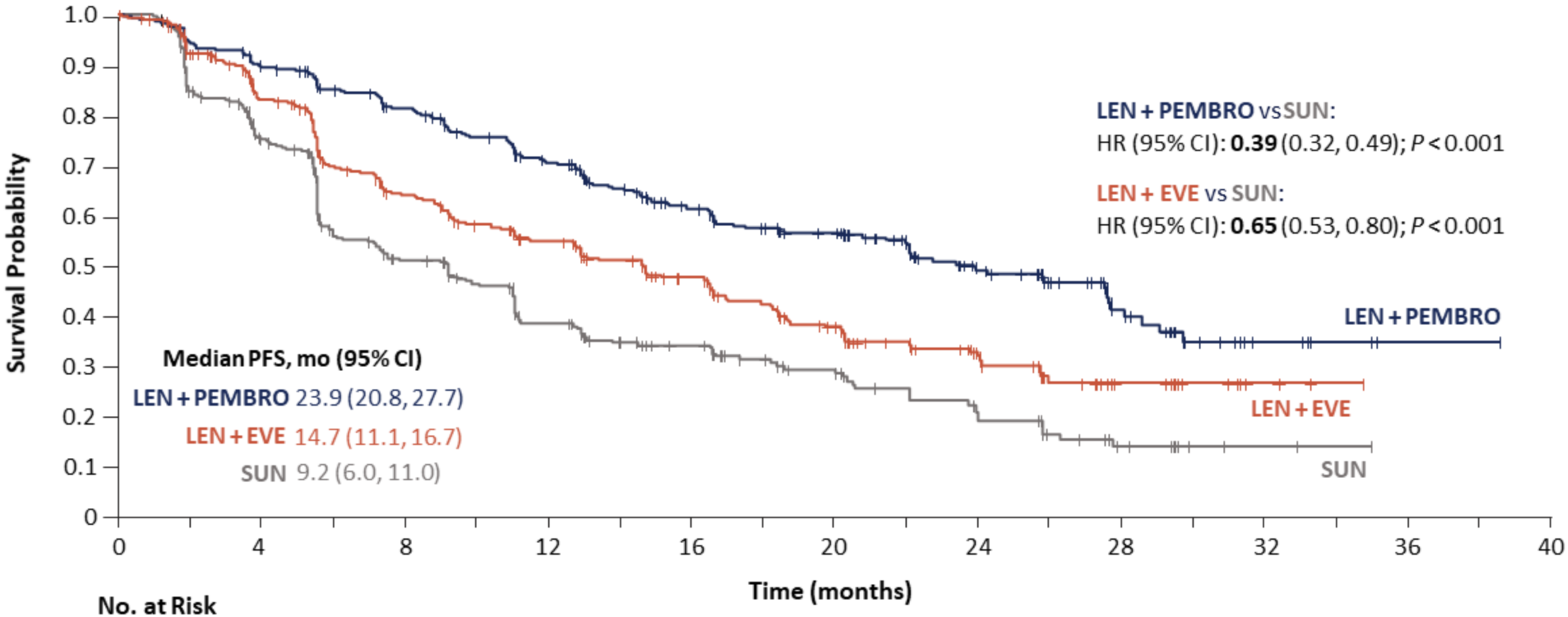
Secondary endpoints

- OS
- ORR by IRC per RECIST v1.1
- Safety
- HRQoL

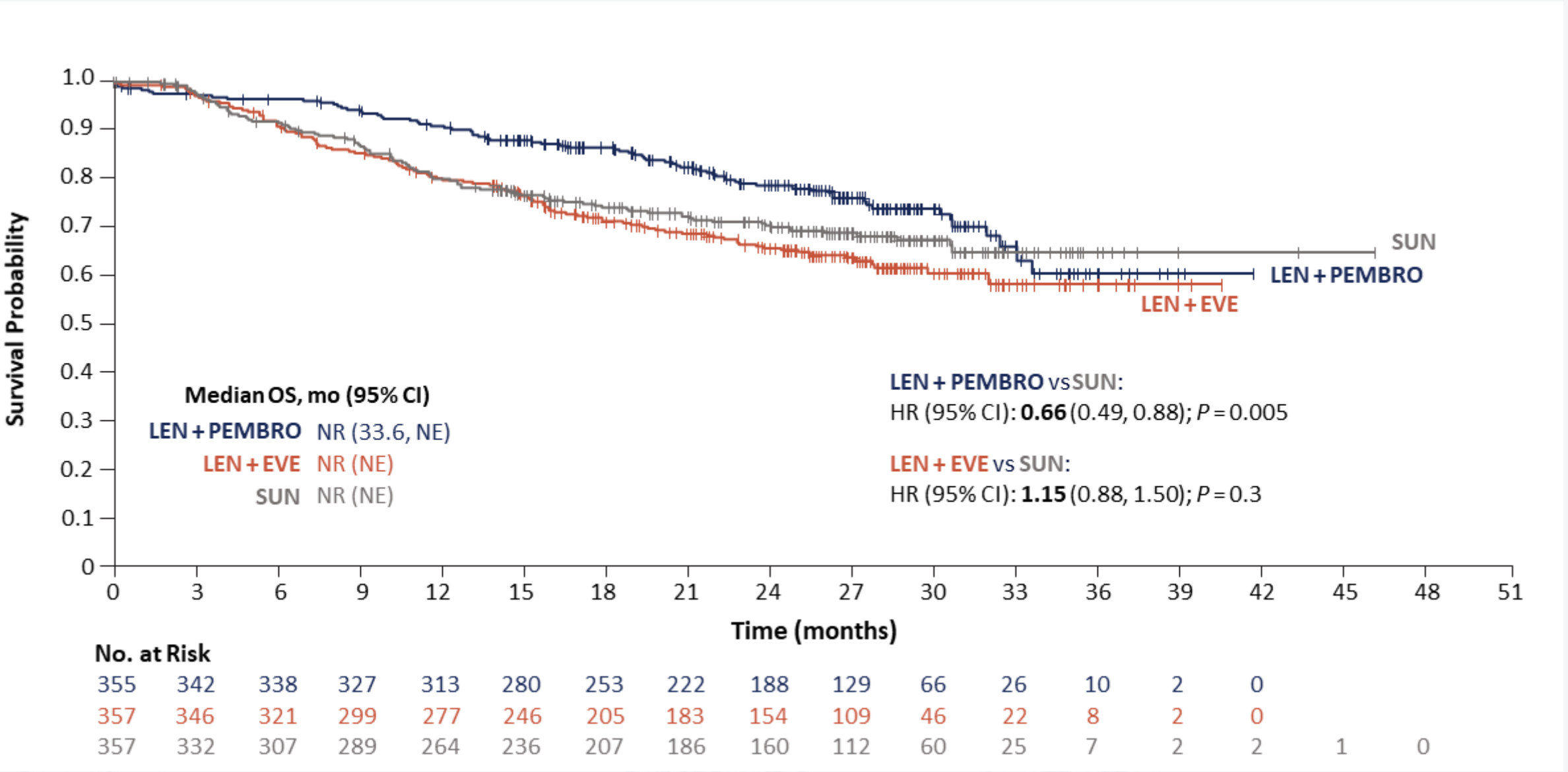
Key exploratory endpoints

- DOR
- Biomarkers

CLEAR: PFS


Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
LEN + PEMBRO vs SUN:
HR (95% CI): 0.39 (0.32, 0.49); P < 0.001
LEN + EVE vs SUN:
HR (95% CI): 0.65 (0.53, 0.80); P < 0.001
LEN + PEMBRO
LEN + EVE
SUN
Median PFS, mo (95% CI)
LEN + PEMBRO 23.9 (20.8, 27.7)
LEN + EVE 14.7 (11.1, 16.7)
SUN 9.2 (6.0, 11.0)
0 4 8 12 16 20 24 28 32 36 40
Time (months)
No. at Risk
355 300 259 213 160 126 80 30 6 1 0
357 259 185 149 105 70 37 13 3 0
357 218 124 85 62 42 25 9 2 0

CLEAR: OS


Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
SUN
LEN + PEMBRO
LEN + EVE
Median OS, mo (95% CI)
LEN + PEMBRO NR (33.6, NE)
LEN + EVE NR (NE)
SUN NR (NE)
LEN + PEMBRO vs SUN:
HR (95% CI): 0.66 (0.49, 0.88); P = 0.005
LEN + EVE vs SUN:
HR (95% CI): 1.15 (0.88, 1.50); P = 0.3
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51
Time (months)
No. at Risk
355 342 338 327 313 280 253 222 188 129 66 26 10 2 0
357 346 321 299 277 246 205 183 154 109 46 22 8 2 0
357 332 307 289 264 236 207 186 160 112 60 25 7 2 2 1 0

CLEAR: ORR

	LEN + PEMBRO (n = 355)	LEN + EVE (n = 357)	SUN (n = 357)
Objective response rate (95% CI) — %	71.0 (66.3–75.7)	53.5 (48.3–58.7)	36.1 (31.2–41.1)
Best overall response — %			
Complete response	16.1	9.8	4.2
Partial response	54.9	43.7	31.9
Stable disease	19.2	33.6	38.1
Progressive disease	5.4	7.3	14.0
Unknown / not evaluable	4.5	5.6	11.8
Relative risk versus SUN (95% CI)	1.97 (1.69–2.29)	1.48 (1.26–1.74)	--
P-value	< 0.001	< 0.001	--

IO + ANTI-VEGF COMBINATIONS: SARCOMATOID FEATURES

	CheckMate-214[1]		CheckMate-9ER[2]		KEYNOTE-456[3]		CLEAR[4]	
	Nivo + Ipi (n= 60)	Sun (n=52)	Nivo + Cabo (n= 34)	Sun (n=41)	Pembro+ Axi (n=51)	Sun (n=54)	Pembro + Lenva (n= 28)	Sun (n=21)
ORR (95% CI), %	56.7 (43.2-69.4)	19.2 (9.6-32.5)	55.9 (37.9-72.8)	22.0 (10.6-37.6)	58.8 (44.2-77.4)	31.5 (19.5-45.6)	60.7	23.8
PFS	0.61 (0.38-0.97)		0.39 (0.22-0.70)		0.54 (0.29-1.00)		0.39 (0.18-0.84)	
OS	0.55 (0.33-0.90)		0.36 (0.16-0.82)		0.58 (0.21-1.59)		0.91 (0.32-2.58)	

1.Motzer, R.J. et al. NEJM 2018;378:1277-90, 2018; 2. Choueiri, T.K. et al. NEJM 384:829-41, 2021; 3. Powles, T et al. *Lancet Oncol* 2020; 21:1563–73, 2020; 4. Motzer, R. et al. NEJM 384:1289-1300, 2021.

IO + ANTI-VEGF COMBINATIONS: ADVERSE EVENTS

	Any Grade	Grade 3, 4, or 5†
Diarrhea	233 (54.3)	39 (9.1)
Hypertension	191 (44.5)	95 (22.1)
Fatigue	165 (38.5)	12 (2.8)
Hypothyroidism	152 (35.4)	1 (0.2)
Decreased appetite	127 (29.6)	12 (2.8)
Palmar–plantar erythrodysesthesia syndrome	120 (28.0)	22 (5.1)

KEYNOTE-426

	Any Grade	Grade ≥3
Any event	319 (99.7)	241 (75.3)
Diarrhea	204 (63.8)	22 (6.9)
Palmar–plantar erythrodysesthesia	128 (40.0)	24 (7.5)
Hypertension	111 (34.7)	40 (12.5)
Hypothyroidism	109 (34.1)	1 (0.3)
Fatigue	103 (32.2)	11 (3.4)
Increased ALT level	90 (28.1)	17 (5.3)
Decreased appetite	90 (28.1)	6 (1.9)

CA209-9ER

	All Grades	Grade ≥3
Patients with any events	432 (99.5)	309 (71.2)
Diarrhea	270 (62.2)	29 (6.7)
Hypertension	215 (49.5)	111 (25.6)
Fatigue	180 (41.5)	15 (3.5)
Nausea	148 (34.1)	6 (1.4)
Palmar–plantar erythrodysesthesia syndrome	145 (33.4)	25 (5.8)

JAVELIN Renal 101

	Any Grade	Grade ≥3†
Any event	351 (99.7)	290 (82.4)
Diarrhea	216 (61.4)	34 (9.7)
Hypertension	195 (55.4)	97 (27.6)
Hypothyroidism‡	166 (47.2)	5 (1.4)
Decreased appetite	142 (40.3)	14 (4.0)
Fatigue	141 (40.1)	15 (4.3)

CLEAR

Motzer RJ, et al. N Engl J Med 2019;380(12):1103.
Rini BI, et al. N Engl J Med 2019;380(12):1116.
Choueiri TK, et al. Ann Oncol 2020;31(suppl_4):S1142.

	PFS			OS		
	Favorable	**Intermedio**	**Pobre**	**Favorable**	**Intermedio**	**Pobre**
Ipi-nivo	2.18 (1.29-3.68)	0.82 (0.64-1.05)		1.45 (0.51-4.12)	0.63 (0.44-0.89)	
Avelu-axi	0.54 (0.32-0.91)	0.74 (0.57-0.95)	0.57 (0.38-0.88)	0.81 (0.33-1.96)	0.86 (0.61-1.20)	0.57 (0.36-0.89)
Pembro-axi	0.81 (0.53-1.24)	0.70 (0.54-0.91)	0.58 (0.35-0.94)	0.64 (0.24-1.68)	0.53 (0.35-0.82)	0.43 (0.23-0.81)
Cabo-nivo	0.62 (0.38-1.01)	0.54 (0.40-0.72)	0.37 (0.37-0.50)	0.84 (0.35-1.97)	0.70 (0.46-1.07)	0.37 (0.21-0.66)
Len/pemb	0.41 (0.28-0.62)	0.39 (0.29-0.52)	0.28 (0.08-0.42)	1.15 (0.55-2.40)	0.72 (0.5-1.05)	0.30 (0.14-0.64)

Rini B. N Engl J Med. 2019 Feb 13;:1–12. Motzer, ESMO 2018Motzer RJ, et al. N Engl J Med 2018;378(14):1277. Choueiri, ESMO 2020. Motzer. ASCO GU 2021

Cortesía Dr Martín Lázaro

	PFS			OS		
	Favorable	Intermedio	Pobre	Favorable	Intermedio	Pobre
Ipi-nivo	2.18 (1.29-3.68)	0.82 (0.64-1.05)		1.45 (0.51-4.12)	0.63 (0.44-0.89)	
Avelu-axi	0.54 (0.32-0.91)	0.74 (0.57-0.95)	0.57 (0.38-0.88)	0.81 (0.33-1.96)	0.86 (0.61-1.20)	0.57 (0.36-0.89)
Pembro-axi	0.81 (0.53-1.24)	0.70 (0.54-0.91)	0.58 (0.35-0.94)	0.64 (0.24-1.68)	0.53 (0.35-0.82)	0.43 (0.23-0.81)
Cabo-nivo	0.62 (0.38-1.01)	0.54 (0.40-0.72)	0.37 (0.37-0.50)	0.84 (0.35-1.97)	0.70 (0.46-1.07)	0.37 (0.21-0.66)
Len/pemb	0.41 (0.28-0.62)	0.39 (0.29-0.52)	0.28 (0.08-0.42)	1.15 (0.55-2.40)	0.72 (0.5-1.05)	0.30 (0.14-0.64)

Rini B. N Engl J Med. 2019 Feb 13;:1–12. Motzer, ESMO 2018Motzer RJ, et al. N Engl J Med 2018;378(14):1277. Choueiri, ESMO 2020. Motzer. ASCO GU 2021

Cortesía Dr Martín Lázaro

PHASE III TRIALS IN FIRST LINE RCC

Control	Comparator(s)	PFS (HR)	OS (HR)
Sunitinib[1]	Nivolumab + Ipilimumab[1]	Yes (0.82)[1]	Yes (0.63)[1]
Sunitinib[2]	Bevacizumab + Atezolizumab[2]	Yes (0.88)[2]	No[2]
Sunitinib[3]	Axitinib + Avelumab[3]	Yes (0.61)[3]	No[3]
Sunitinib[4]	Axitinib + Pembrolizumab[4]	Yes (0.69)[4]	Yes (0.59)[4]
Sunitinib[5]	Cabozantinib + Nivolumab[5]	Yes (0.51)[5]	Yes (0.60)[5]
Sunitinib[6]	Lenvatinib + Everolimus vs Lenva + Pembro[6]	Yes (0,39)[6]	Yes (0,66)[6]
Nivo + Ipi[7]	Cabozantinib + Nivolumab + Ipilimumab[7]	Active, not recruiting[7]	

1. Motzer RJ, et al. *N Engl J Med* 2018; 2. Rini BI, et al. *Lancet* 2019; 3. Motzer RJ, et al. *N Engl J Med* 2019; 4. Rini ER, et al. *N Engl J Med* 2019; 5. Choueiri T et al. ESMO 2020; 6. Motzer R, *N Engl J Med* 2021; 7. Available at: clinicaltrials.gov..

PHASE III TRIALS IN FIRST LINE RCC

Control	Comparator(s)	PFS (HR)	OS (HR)
Sunitinib[1]	**Nivolumab + Ipilimumab[1]**	**Yes (0.82)[1]**	**Yes (0.63)[1]**
Sunitinib[2]	Bevacizumab + Atezolizumab[2]	Yes (0.88)[2]	No[2]
Sunitinib[3]	**Axitinib + Avelumab[3]**	**Yes (0.61)[3]**	**No[3]**
Sunitinib[4]	**Axitinib + Pembrolizumab[4]**	**Yes (0.69)[4]**	**Yes (0.59)[4]**
Sunitinib[5]	**Cabozantinib + Nivolumab[5]**	**Yes (0.51)[5]**	**Yes (0.60)[5]**
Sunitinib[6]	**Lenvatinib + Everolimus vs Lenva + Pembro[6]**	**Yes (0,39)[6]**	**Yes (0,66)[6]**
Nivo + Ipi[7]	Cabozantinib + Nivolumab + Ipilimumab[7]	Active, not recruiting[7]	

1. Motzer RJ, et al. *N Engl J Med* 2018; 2. Rini BI, et al. *Lancet* 2019; 3. Motzer RJ, et al. *N Engl J Med* 2019; 4. Rini ER, et al. *N Engl J Med* 2019; 5. Choueiri T et al. ESMO 2020; 6. Motzer R, *N Engl J Med* 2021; 7. Available at: clinicaltrials.gov..

PHASE III TRIALS IN FIRST LINE RCC

Control	Comparator(s)	PFS (HR)	OS (HR)
Sunitinib[1]	**Nivolumab + Ipilimumab[1]**	**Yes (0.82)[1]**	**Yes (0.63)[1]**
Sunitinib[2]	Bevacizumab + Atezolizumab[2]	Yes (0.88)[2]	No[2]
Sunitinib[3]	**Axitinib + Avelumab[3]**	**Yes (0.61)[3]**	**No[3]**
Sunitinib[4]	**Axitinib + Pembrolizumab[4]**	**Yes (0.69)[4]**	**Yes (0.59)[4]**
Sunitinib[5]	**Cabozantinib + Nivolumab[5]**	**Yes (0.51)[5]**	**Yes (0.60)[5]**
Sunitinib[6]	**Lenvatinib + Everolimus vs Lenva + Pembro[6]**	**Yes (0,39)[6]**	**Yes (0,66)[6]**
Nivo + Ipi[7]	Cabozantinib + Nivolumab + Ipilimumab[7]	Active, not recruiting[7]	

1. Motzer RJ, et al. *N Engl J Med* 2018; 2. Rini BI, et al. *Lancet* 2019; 3. Motzer RJ, et al. *N Engl J Med* 2019; 4. Rini ER, et al. *N Engl J Med* 2019; 5. Choueiri T et al. ESMO 2020; 6. Motzer R, *N Engl J Med* 2021; 7. Available at: clinicaltrials.gov..

FIRST LINE TRIALS COMPARISON

	CheckMate 214 ITT (n=550 *vs* n=546)	KEYNOTE-426 ITT (n=432 *vs* n=429)	CheckMate 9ER ITT (n=323 *vs* n=328)	CLEAR ITT (n=355 *vs* n=357)
Primary endpoint	OS, PFS and ORR among intermediate and poor-risk patients	OS, PFS in ITT population	PFS in ITT population	PFS in ITT population
Med f/u, months	43.6	30.6	18.1	27.0
Prognostic risk, %				
Favorable	23	32	23	31
Intermediate	61	55	58	59
Poor	17	13	19	9
PD-L1 status ≥1%, %	23	56	26	30

FIRST LINE TRIALS COMPARISON

	CheckMate 214 ITT (n=550 *vs* n=546)	KEYNOTE-426 ITT (n=432 *vs* n=429)	CheckMate 9ER ITT (n=323 *vs* n=328)	CLEAR ITT (n=355 *vs* n=357)
mOS, months **HR (CI);** **P-value**	NR *vs* 38.4 0.72 (0.61-0.86) 0.0002	NR *vs* 35.7 0.68 (0.55-0.85) <0.001	NR *vs* NR 0.60 (0.40-0.89) 0.001	NR *vs* NR 0.66 (0.49-0.88) 0.005
mPFS, months **HR (CI);** **p value**	12.4 *vs* 12.3 0.88 (0.75-1.04) 0.127 (NS)	15.4 *vs* 11.1 0.71 (0.60-0.84) <0.0001	16.6 *vs* 8.3 0.51 (0.41-0.64) <0.0001	23.9 *vs* 9.2 0.39 (0.32-0.49) <0.001
ORR, % **p value**	39 *vs* 33 0.02	60 *vs* 40 <0.0001	56 *vs* 27 <0.0001	71 *vs* 36 <0.001
CR, %	11 *vs* 2	9 *vs* 3	8 *vs* 5	16 *vs* 4
PD, %	17.6 *vs* 14.1	11.3 *vs* 17.2	5.6 *vs* 13.2	5.4 *vs* 14.0
mDOR, months	NR *vs* 18.2	23.5 *vs* 15.9	20.2 *vs* 11.5	25.8 *vs* 14.6

FIRST LINE TRIALS COMPARISON

	CheckMate 214 ITT (n=550 *vs* n=546)	KEYNOTE-426 ITT (n=432 *vs* n=429)	CheckMate 9ER ITT (n=323 *vs* n=328)	CLEAR ITT (n=355 *vs* n=357)
mOS, months **HR (CI);** **P-value**	NR *vs* 38.4 0.72 (0.61-0.86) 0.0002	NR *vs* 35.7 0.68 (0.55-0.85) <0.001	NR *vs* NR 0.60 (0.40-0.89) 0.001	NR *vs* NR 0.66 (0.49-0.88) 0.005
mPFS, months **HR (CI);** **p value**	12.4 *vs* 12.3 0.88 (0.75-1.04) 0.127 (NS)	15.4 *vs* 11.1 0.71 (0.60-0.84) <0.0001	16.6 *vs* 8.3 0.51 (0.41-0.64) <0.0001	23.9 *vs* 9.2 0.39 (0.32-0.49) <0.001
ORR, % **p value**	39 *vs* 33 0.02	60 *vs* 40 <0.0001	56 *vs* 27 <0.0001	71 *vs* 36 <0.001
CR, %	11 *vs* 2	9 *vs* 3	8 *vs* 5	16 *vs* 4
PD, %	17.6 *vs* 14.1	11.3 *vs* 17.2	5.6 *vs* 13.2	5.4 *vs* 14.0
mDOR, months	NR *vs* 18.2	23.5 *vs* 15.9	20.2 *vs* 11.5	25.8 *vs* 14.6

CONCLUSIONS

- Three different combinations have demonstrated an increase in OS in first line RCC with IO-TKI combinations:
  - **KEYNOTE-426: Pembrolizumab+Axitinib**
  - **CHECKMATE-9ER: Nivolumab-Cabozantinib**
  - **CLEAR: Pebrolizumab-Lenvatinib**
- Important differences:
  - Different endpoints
  - Definition of PDL1+ differs across the studies
- Need further follow-up and well designed phase 3 trials and standarized biomarkers.
- Need biomarker guided studies!!!

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Gracias

ARÁN