Advanced Renal Cell Carcinoma

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Medical Oncology Department

Jules Bordet Institute

OUTLINE

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1. **Current first line management in advanced renal cell carcinoma**

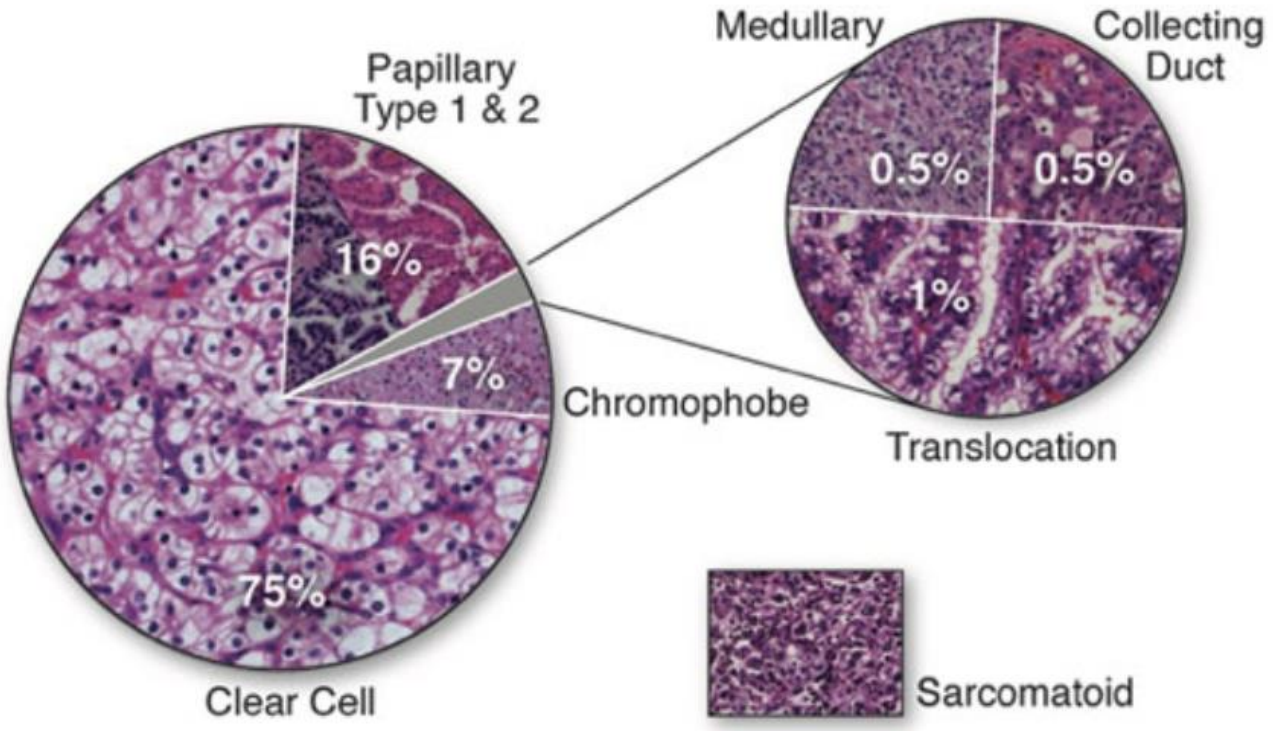
2. **How to select patients for 1st line treatment ?**

3. **Subsequent therapies**

4. **Future perspectives for 1st line treatment**

INTRODUCTION

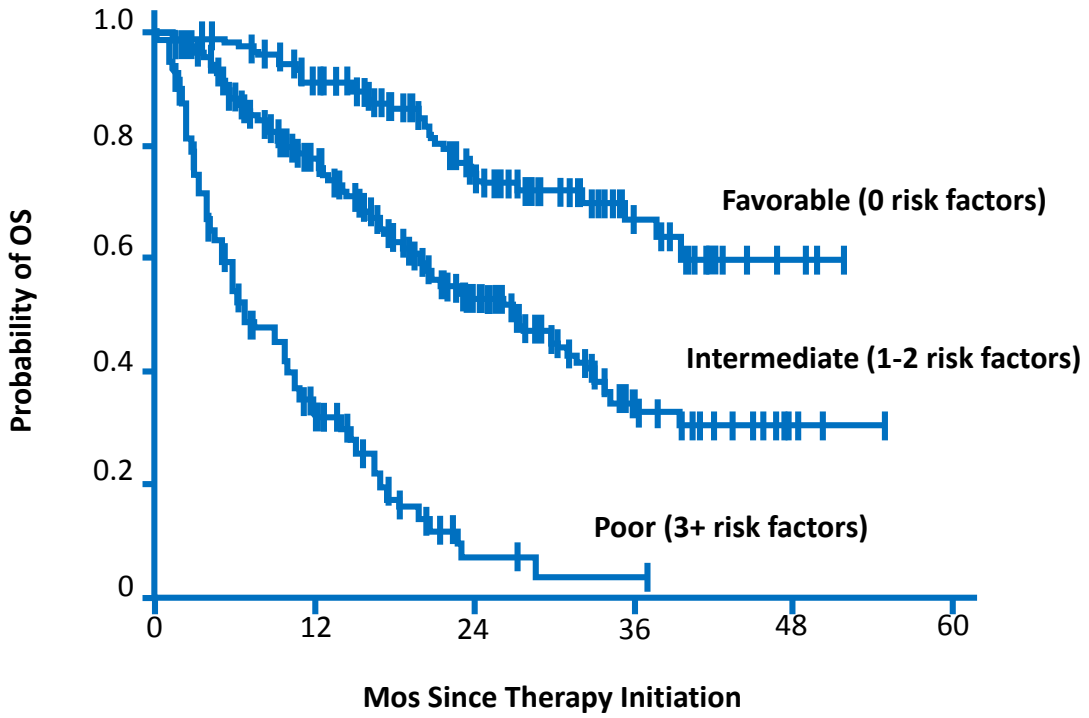
- **Renal cell carcinoma (RCC) is a heterogeneous group** of diseases



Clear cell represents 75% of RCC (ccRCC)

Sarcomatoid features can be found in all RCC subtypes

IMDC CRITERIA



Clinical:

- KPS < 80%,
- Time from diagnosis to tx < 1 yr

Laboratory:

- Hemoglobin < LLN,
- Calcium > ULN,
- Neutrophil count > ULN,
- Platelet count > ULN

75% to 80% of patients are classified as intermediate or poor risk

Heng. JCO. 2009;27:5794.

FIRST LINE IN RENAL CELL CARCINOMA

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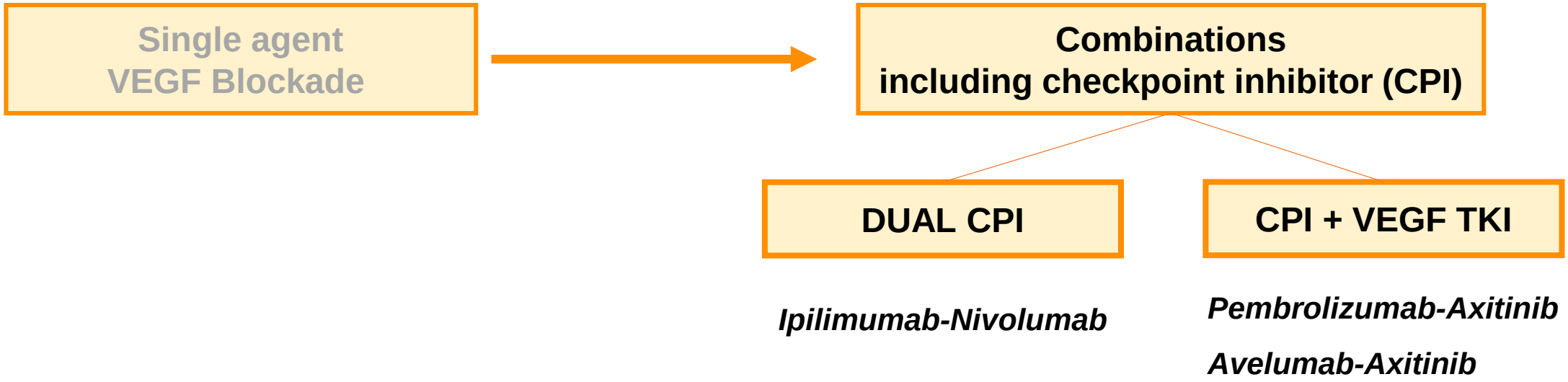
- **Impressive progress in last years**



PHASE III TRIALS IN TREATMENT NAIVE ccRCC

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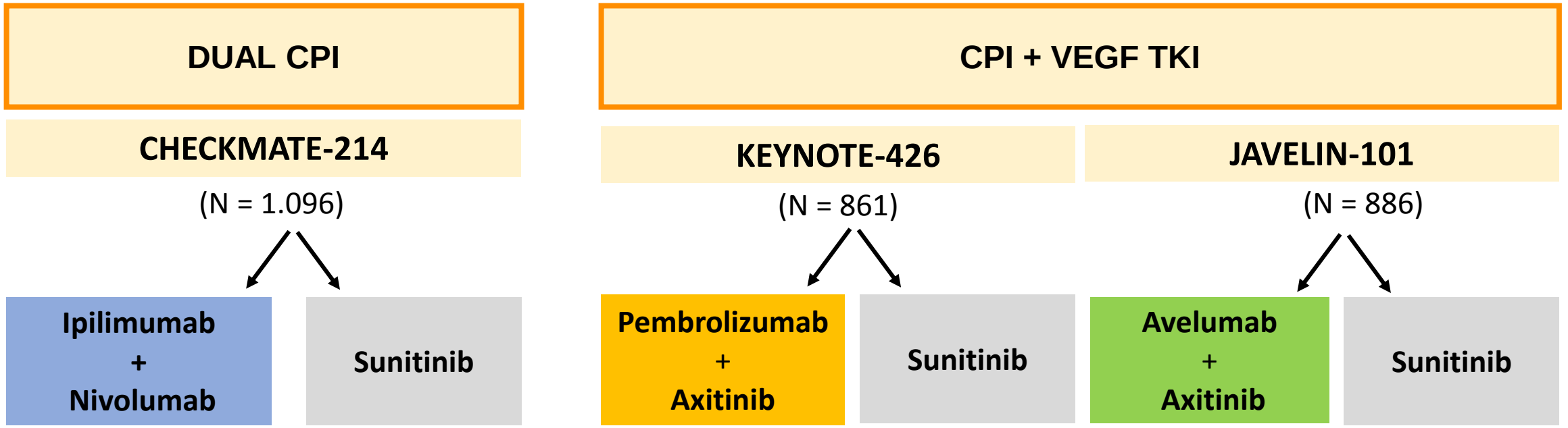

PHASE III TRIALS IN TREATMENT NAIVE ccRCC

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DUAL CPI

CHECKMATE-214

(N = 1.096)

- **Ipilimumab + Nivolumab**
- **Sunitinib**

Primary objectives:
- PFS in intermediate/poor risk
- OS in intermediate/poor risk
- ORR in intermediate/poor risk

CPI + VEGF TKI

KEYNOTE-426

(N = 861)

- **Pembrolizumab + Axitinib**
- **Sunitinib**

Primary objectives:
- PFS in ITT
- OS in ITT

JAVELIN-101

(N = 886)

- **Avelumab + Axitinib**
- **Sunitinib**

Primary objectives:
- PFS in PD-L1+
- OS in PD-L1+

PHASE III TRIALS IN TREATMENT NAIVE ccRCC

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DUAL CPI

CHECKMATE-214

(N = 1.096)

- Ipilimumab + Nivolumab
- Sunitinib

- Favorable IMDC: 23%
- PD-L1+: 23%
- Median FU: 30 mos

CPI + VEGF TKI

KEYNOTE-426

(N = 861)

- Pembrolizumab + Axitinib
- Sunitinib

- Favorable IMDC: 31%
- PD-L1+: 61%
- Median FU: 13 mos

JAVELIN-101

(N = 886)

- Avelumab + Axitinib
- Sunitinib

- Favorable IMDC: 21%
- PD-L1+: 63%
- Median FU: 10 mos

PHASE III TRIALS IN TREATMENT NAIVE ccRCC

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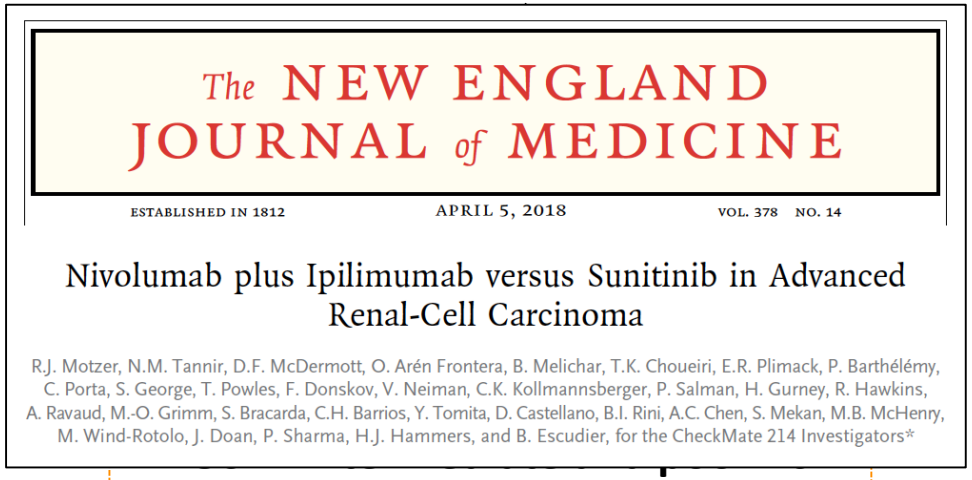
DUAL CPI

CHECKMATE-214

(N = 1.096)



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*

CPI + VEGF TKI

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- OS in ITT

JAVELIN-101

(N = 886)

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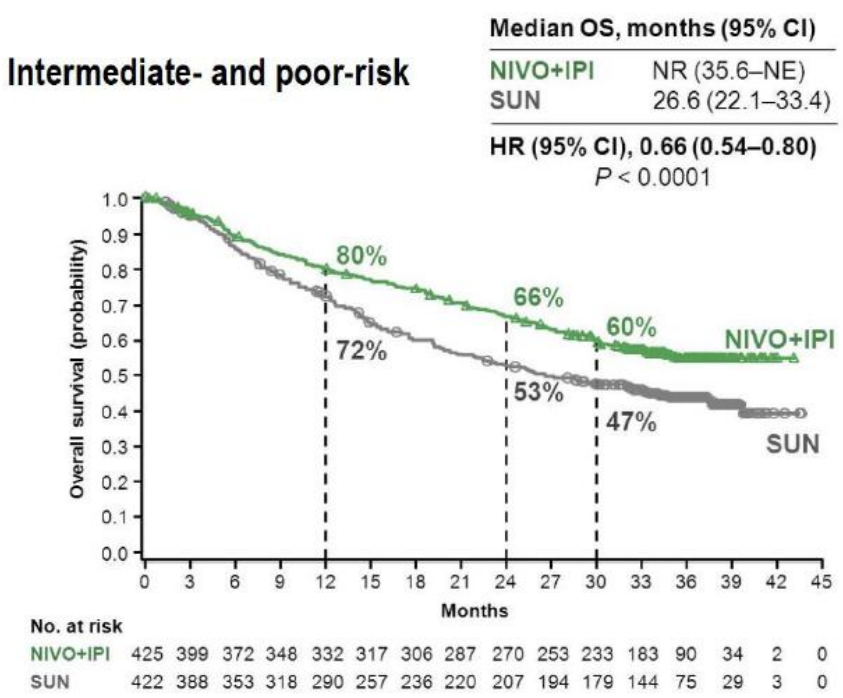
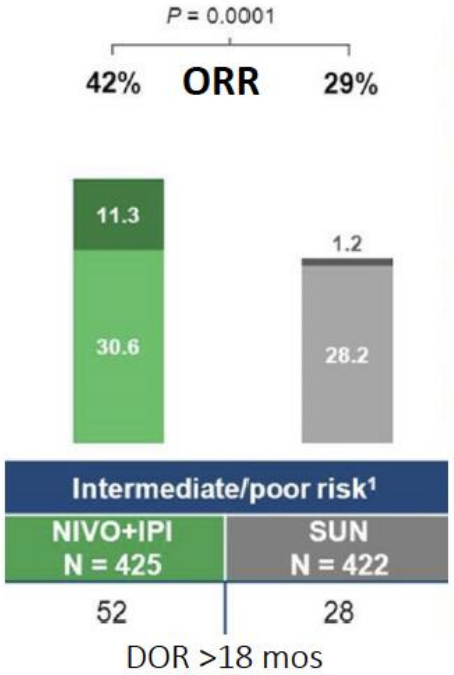
- **Sunitinib**

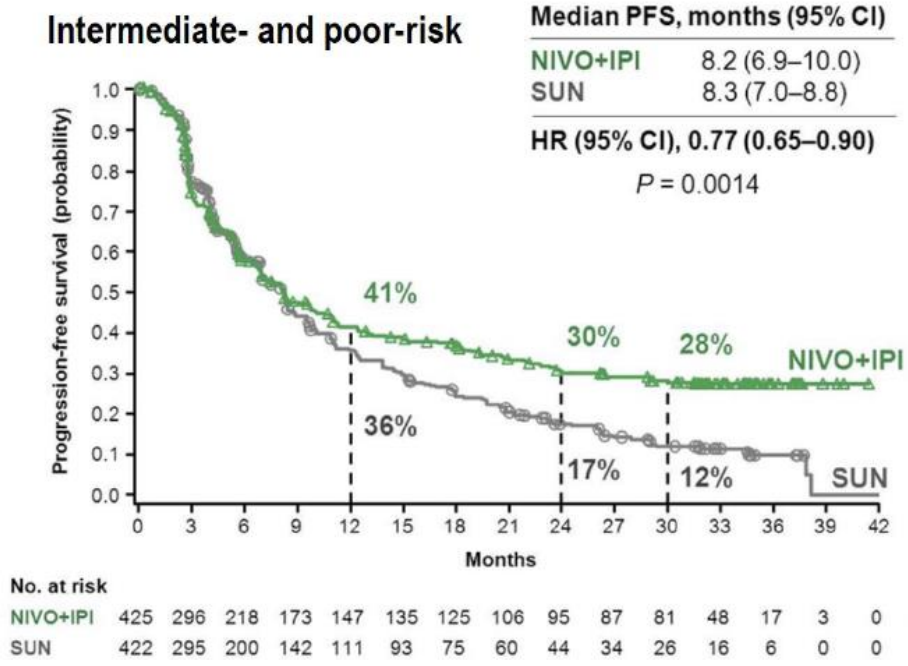
- PFS in PD-L1+
- OS in PD-L1+

CHECKMATE-214: IPI – NIVO IN 1ST LINE

INTERMEDIATE AND POOR IMDC RISK GROUP



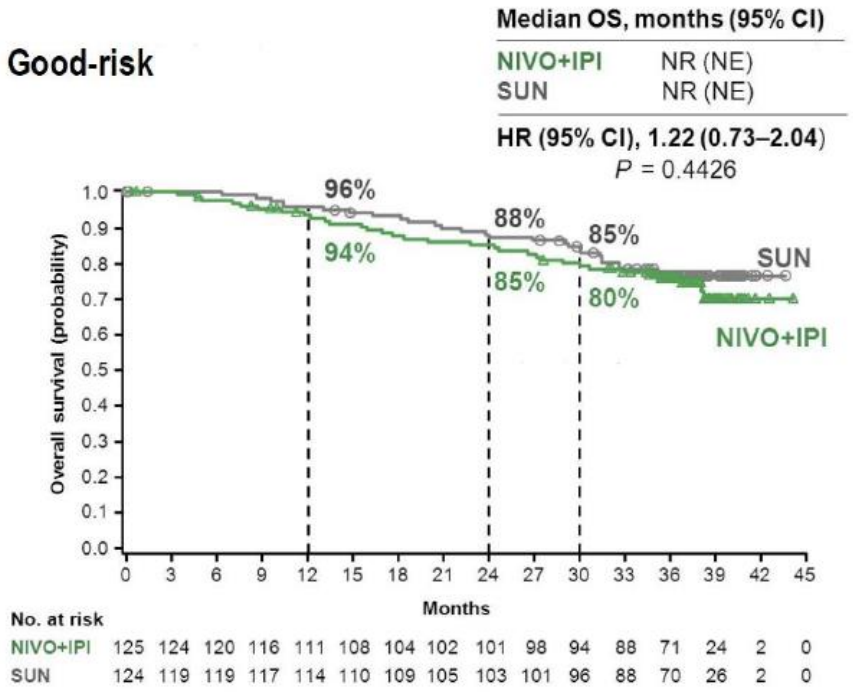


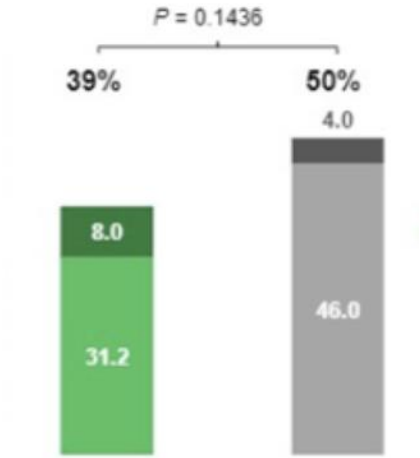


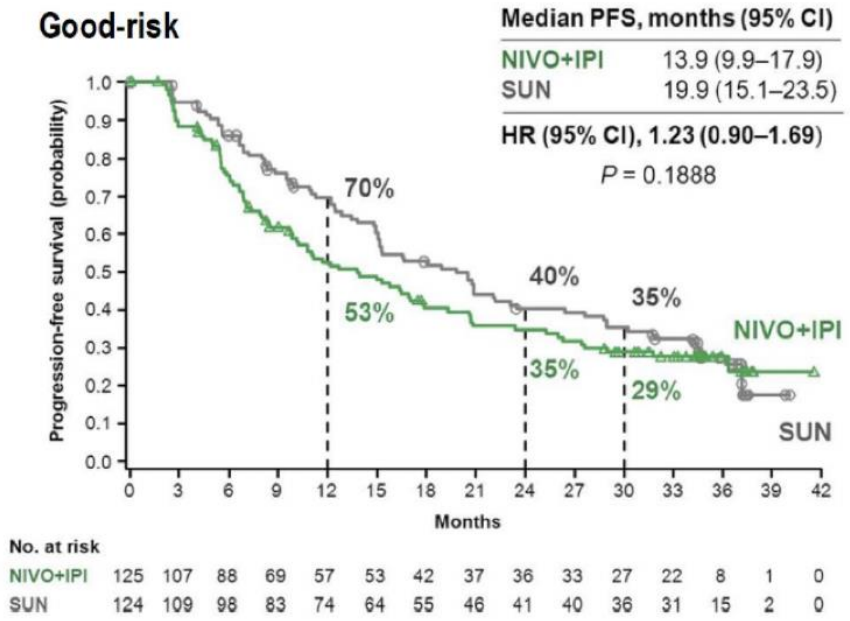
Motzer RJ, et al. N Engl J Med 2018; Motzer RJ, et al. Lancet Oncol 2019

CHECKMATE-214: IPI – NIVO IN 1ST LINE

GOOD IMDC RISK GROUP







Patients with favorable risk represented 23% in each arm

Motzer RJ, et al. N Engl J Med 2018; Motzer RJ, et al. Lancet Oncol 2019

PHASE III TRIALS IN TREATMENT NAIVE ccRCC

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DUAL CPI

CHECKMATE-214

(N = 1.096)

- **Ipilimumab + Nivolumab**
- **Sunitinib**

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- OS in intermediate/poor risk
- ORR in intermediate/poor risk

CPI + VEGF TKI

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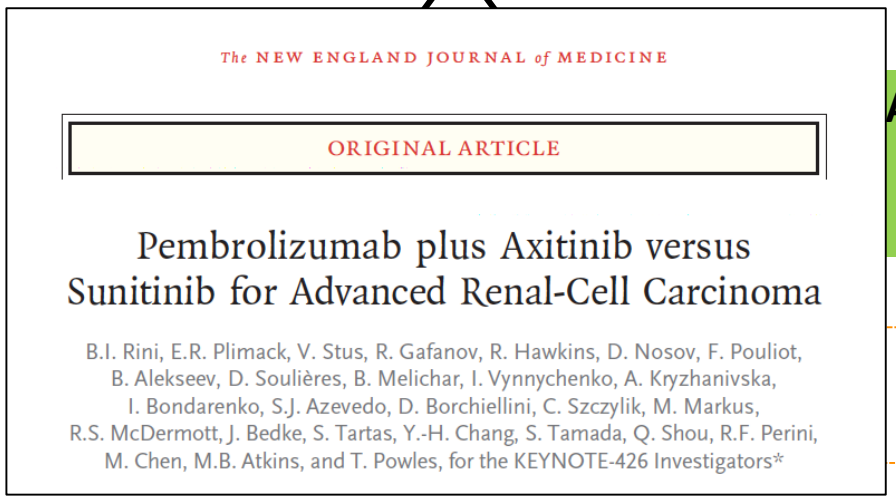

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

B.I. Rini, E.R. Plimack, V. Stus, R. Gafanov, R. Hawkins, D. Nosov, F. Pouliot, B. Alekseev, D. Soulières, B. Melichar, I. Vynnychenko, A. Kryzhanivska, I. Bondarenko, S.J. Azevedo, D. Borchiellini, C. Szczylik, M. Markus, R.S. McDermott, J. Bedke, S. Tartas, Y.-H. Chang, S. Tamada, Q. Shou, R.F. Perini, M. Chen, M.B. Atkins, and T. Powles, for the KEYNOTE-426 Investigators*

JAVELIN-101

(N = 886)

- **Avelumab + Axitinib**
- **Sunitinib**

PFS in PD-L1+
OS in PD-L1+

KEYNOTE-426: PEMBRO + AXITINIB IN 1ST LINE

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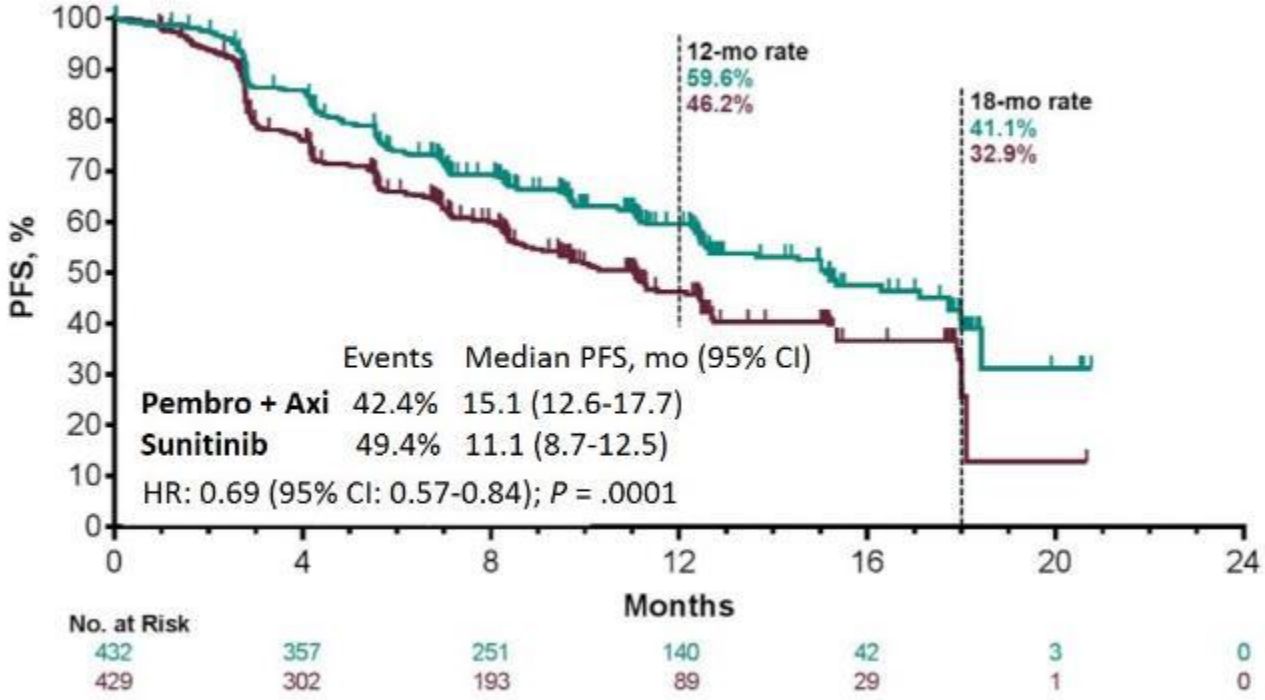
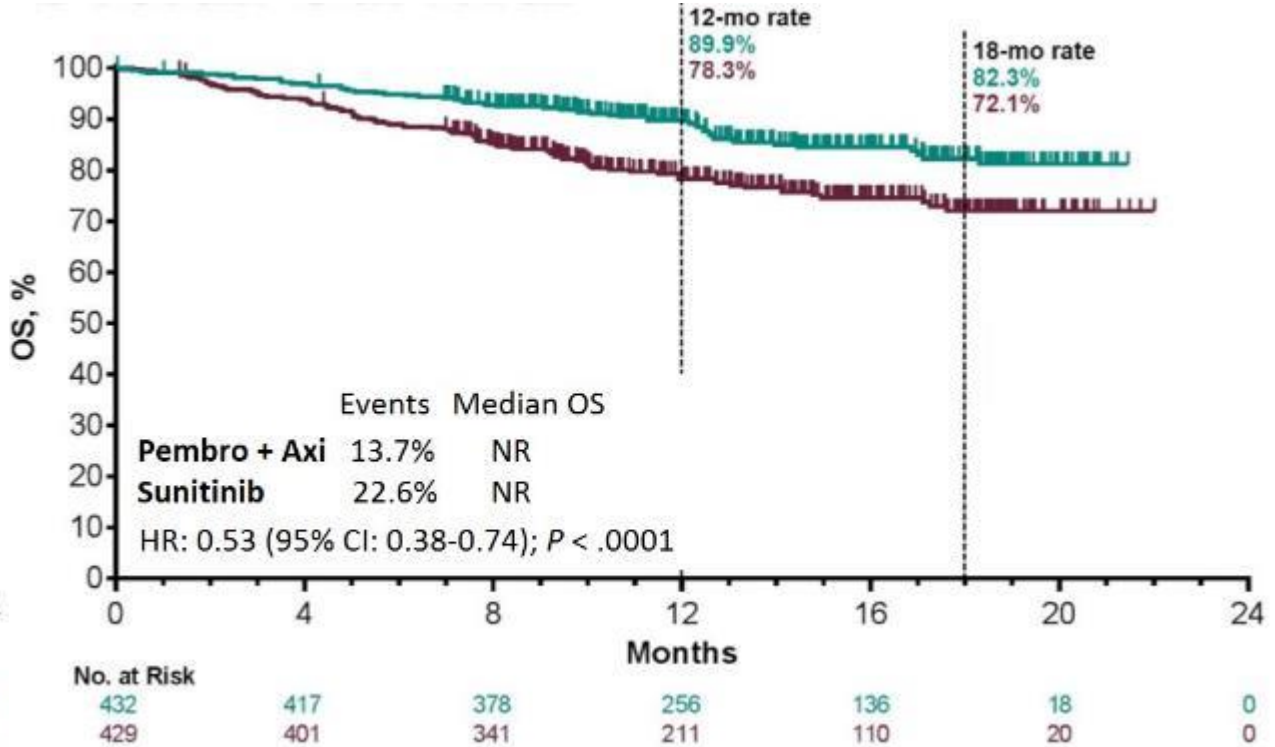
PFS in ITT Cohort



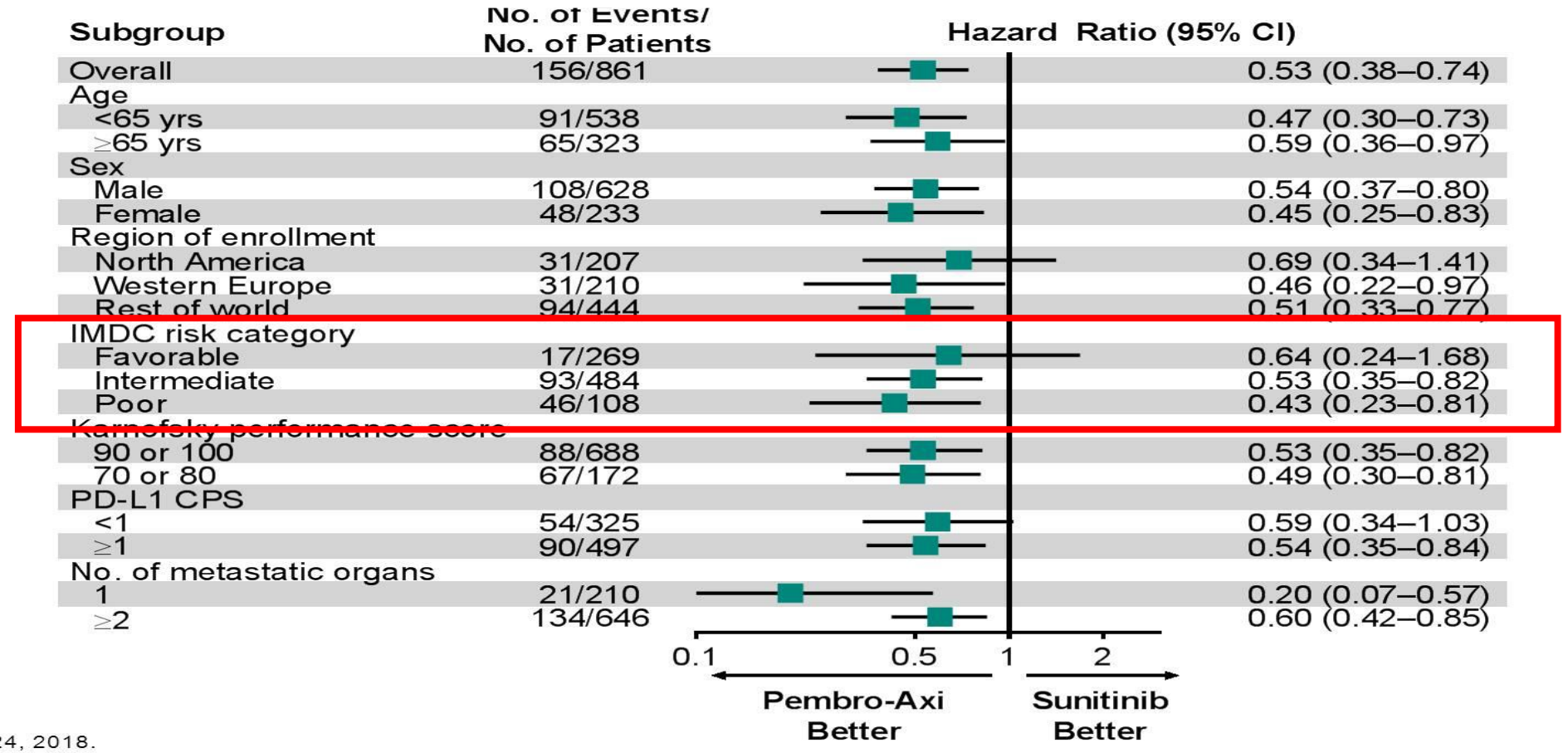
OS in ITT Cohort



Rini et al. N Engl J Med 2019

KEYNOTE-426: PEMBRO + AXITINIB IN 1ST LINE

OS by subgroups



Data cutoff date: Aug 24, 2018.

Rini et al. N Engl J Med 2019

KEYNOTE-426: PEMBRO + AXITINIB IN 1ST LINE

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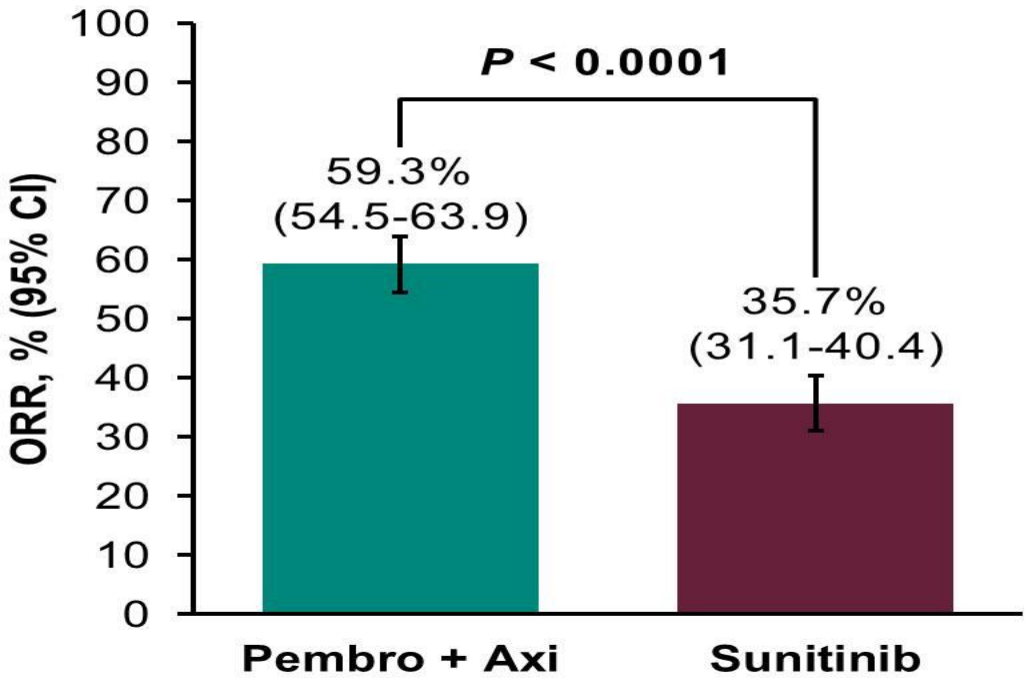
ORR in ITT cohort



Best Response	Pembro + Axi N = 432	Sunitinib N = 429
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%)
NE[a]	8 (1.9%)	6 (1.4%)
NA[b]	15 (3.5%)	28 (6.5%)
Response Duration	**N = 256**	**N = 153**
Median (range), mo	NR (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

[a]Patients who had ≥1 post-baseline imaging assessment, none of which were evaluable per RECIST v1.1 by BICR. [b]Patients who did not have ≥1 post-baseline imaging assessment.
Data cutoff date: Aug 24, 2018.

Rini et al. N Engl J Med 2019

PHASE III TRIALS IN TREATMENT NAIVE ccRCC

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CHECKMATE-214

(N = 1.096)

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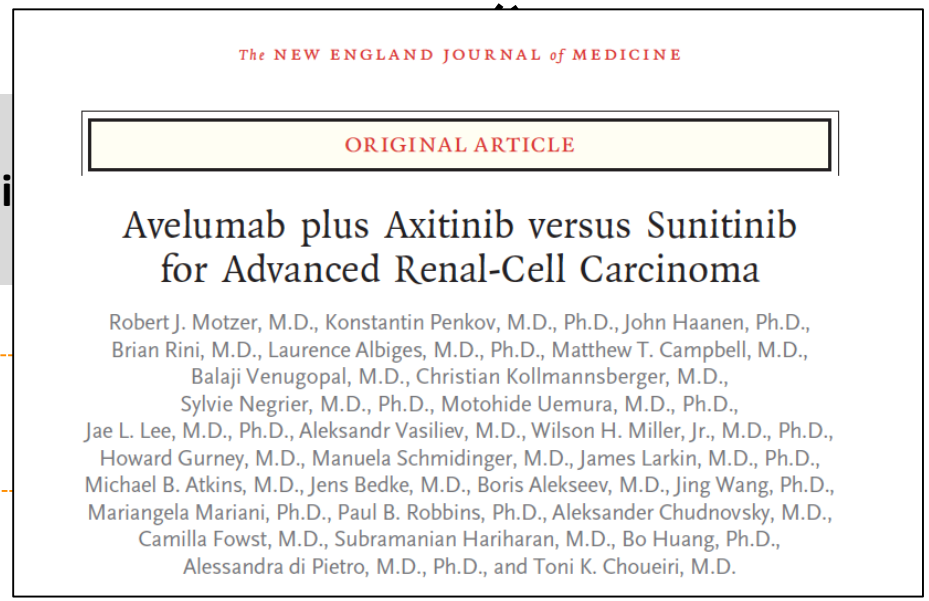

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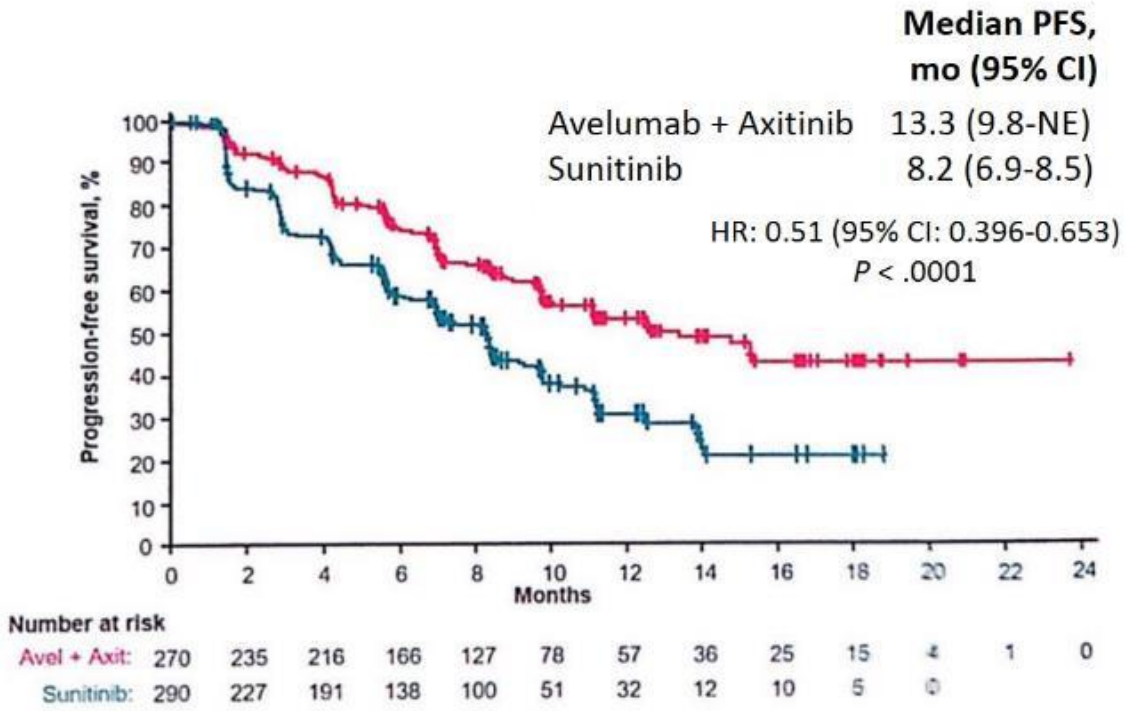
Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

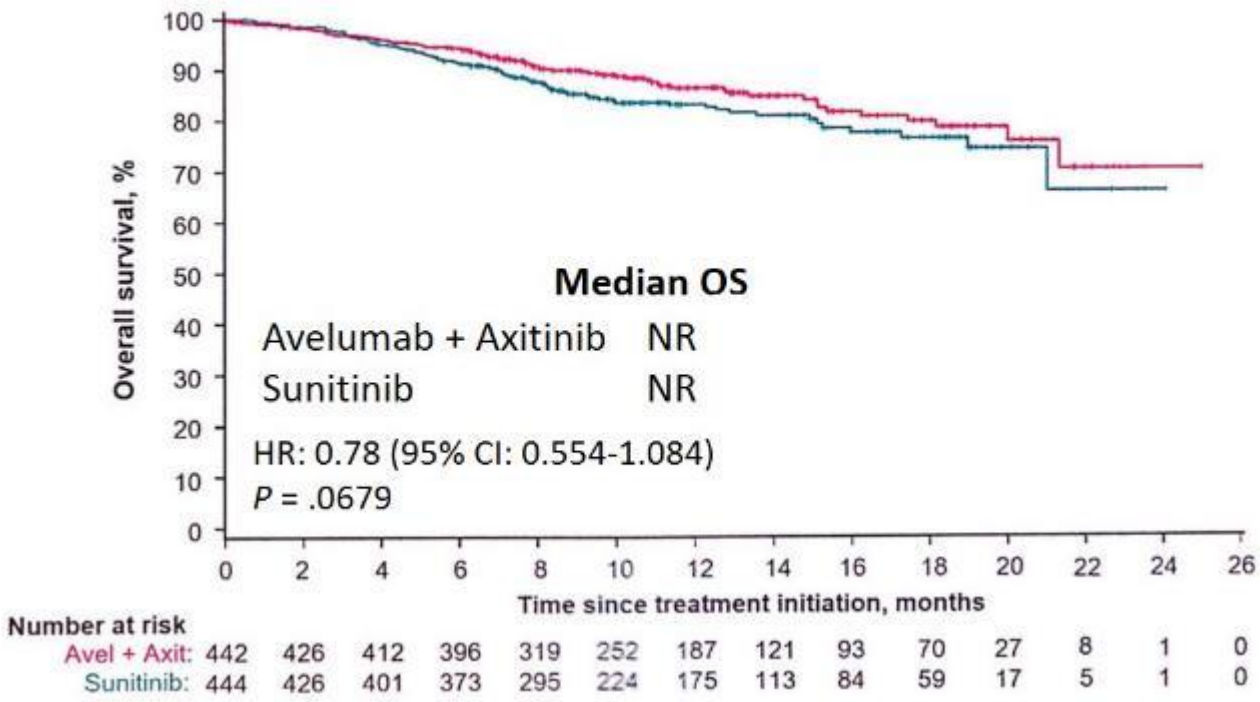
Robert J. Motzer, M.D., Konstantin Penkov, M.D., Ph.D., John Haanen, Ph.D., Brian Rini, M.D., Laurence Albiges, M.D., Ph.D., Matthew T. Campbell, M.D., Balaji Venugopal, M.D., Christian Kollmannsberger, M.D., Sylvie Negrier, M.D., Ph.D., Motohide Uemura, M.D., Ph.D., Jae L. Lee, M.D., Ph.D., Aleksandr Vasiliev, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Howard Gurney, M.D., Manuela Schmidinger, M.D., James Larkin, M.D., Ph.D., Michael B. Atkins, M.D., Jens Bedke, M.D., Boris Alekseev, M.D., Jing Wang, Ph.D., Mariangela Mariani, Ph.D., Paul B. Robbins, Ph.D., Aleksander Chudnovsky, M.D., Camilla Fowst, M.D., Subramanian Hariharan, M.D., Bo Huang, Ph.D., Alessandra di Pietro, M.D., Ph.D., and Toni K. Choueiri, M.D.

JAVELIN-101: AVELUMAB + AXITINIB IN 1ST LINE

PFS in PD-L1+ Cohort



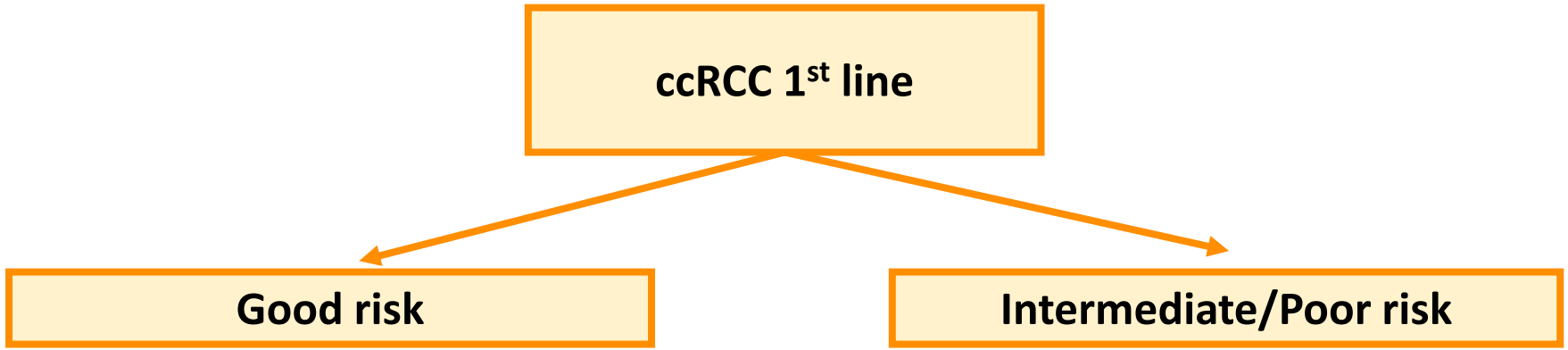
OS in PD-L1+



Also significantly PFS benefit in ITT
Benefit irrespective of the IMDC risk

Motzer et al. N Engl J Med 2019

FIRST LINE IN RCC



Axitinib + Pembrolizumab
Axitinib + Avelumab

Nivolumab + Ipilimumab
Axitinib + Pembrolizumab
Axitinib + Avelumab

OUTLINE

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1. Current first line management in advanced renal cell carcinoma

2. How to select patients for 1st line treatment ?

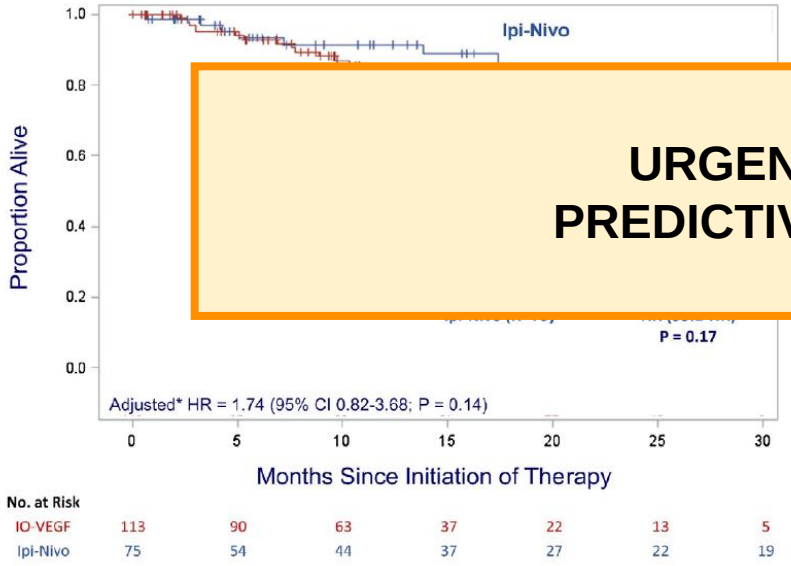
3. Subsequent therapies

4. Future perspectives for 1st line treatment

HOW TO SELECT PATIENTS FOR 1ST LINE IN RCC

- **Not recommendable to make direct comparisons between studies**

- **Retrospective data**
  - Compared patients treated in 1st line with Ipi-Nivo (n=75) versus IO+VEGF TKI (n=113)



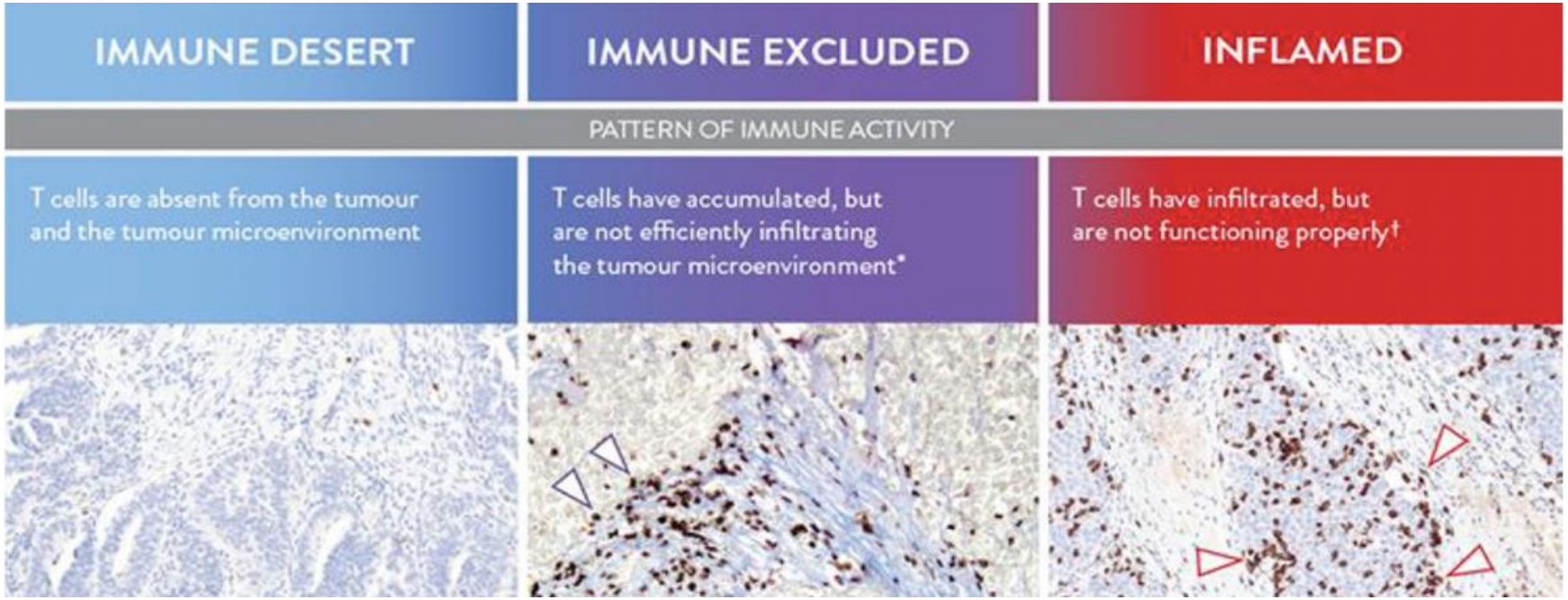
OS of 1st line IO combos (IO-VEGF vs Ipi-Nivo)

TTF of 2nd line VEGFR-TKIs after 1st line IO combos

URGENT NEED FOR PREDICTIVE BIOMARKERS

Dudani et al. Eur Urol 2019

IMDC MODEL RISK



VEGFi — **IMMUNOTHERAPY**

Synergistic activity ?

FAVORABLE RISK IMDC	***INTERMEDIATE/ POOR***
Angiogenesis gene expression	

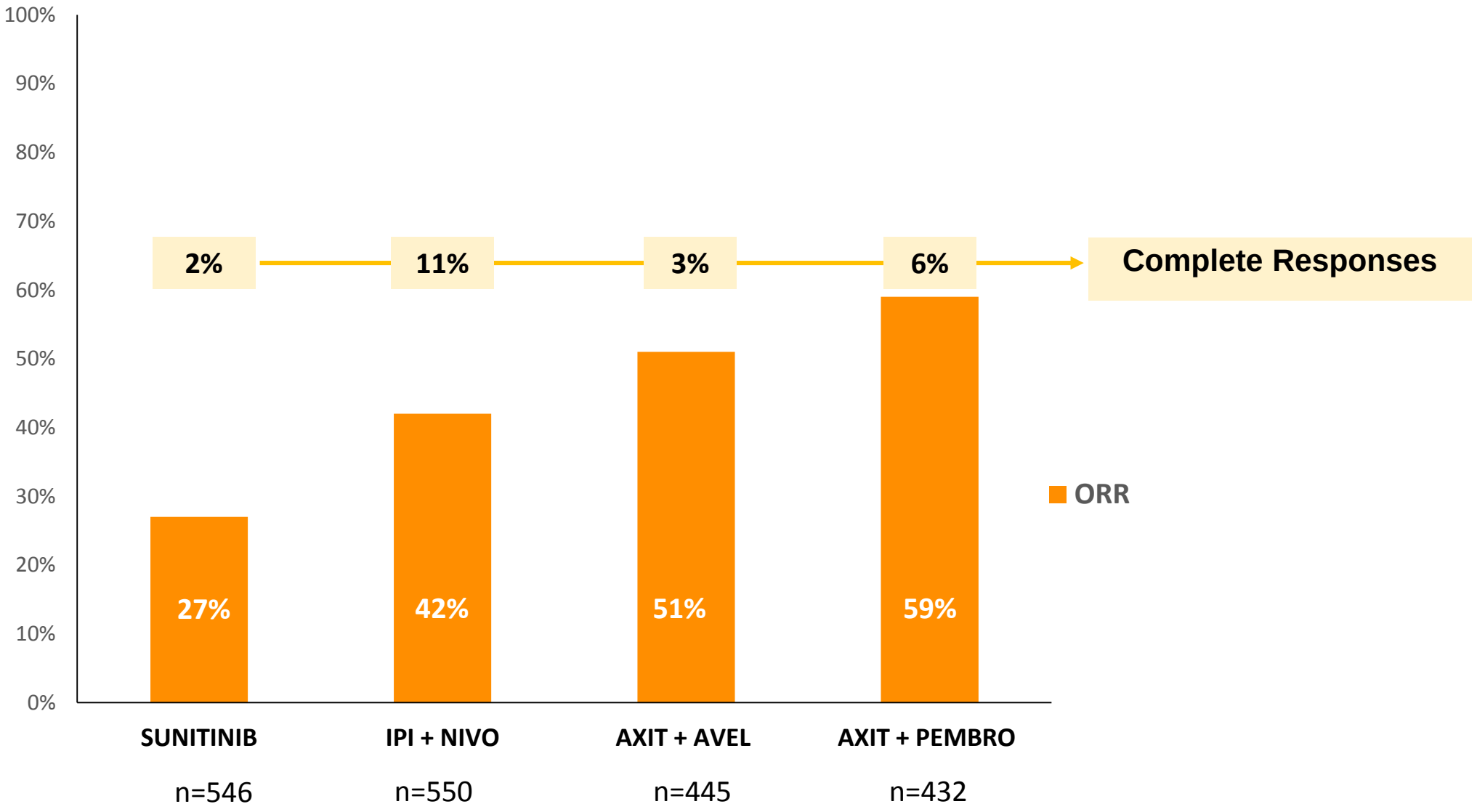
PD-L1 EXPRESSION

Ventana PD-L1 IHC SP263 assay	Positive immune cells within the tumor area		Ave + Axi vs Sun
PD-L1status:			
Positive	106/270	145/290	0.63 (0.487, 0.805)
Negative	54/132	58/120	0.80 (0.551, 1.164)
Not evaluable	18/40	13/34	0.83 (0.403, 1.699)

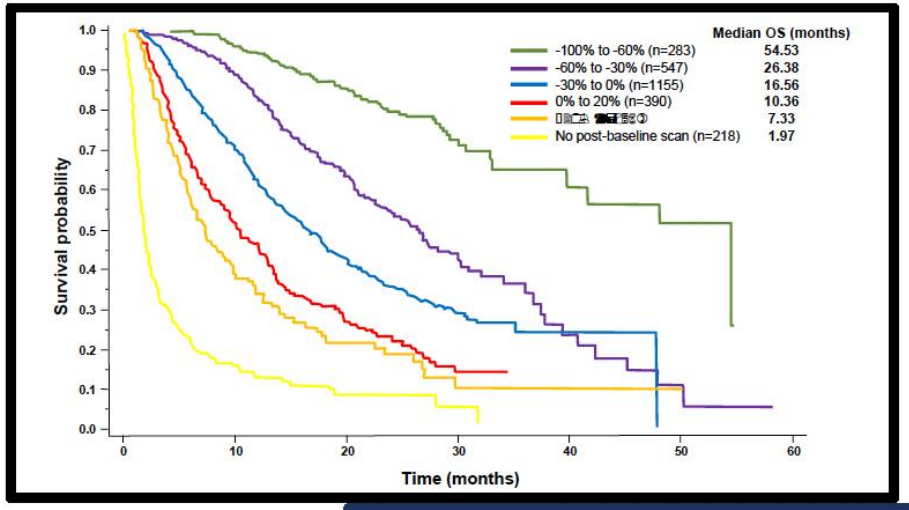
Agilent PD-L1 22C3 pharmDX assay	Combined score (no. of PD-L1+ cells/total no. of tumor cells)		Pembro + Axi vs Sun
PD-L1 combined positive score			
<1	54/325		0.59 (0.34–1.03)
≥1	90/497		0.54 (0.35–0.84)

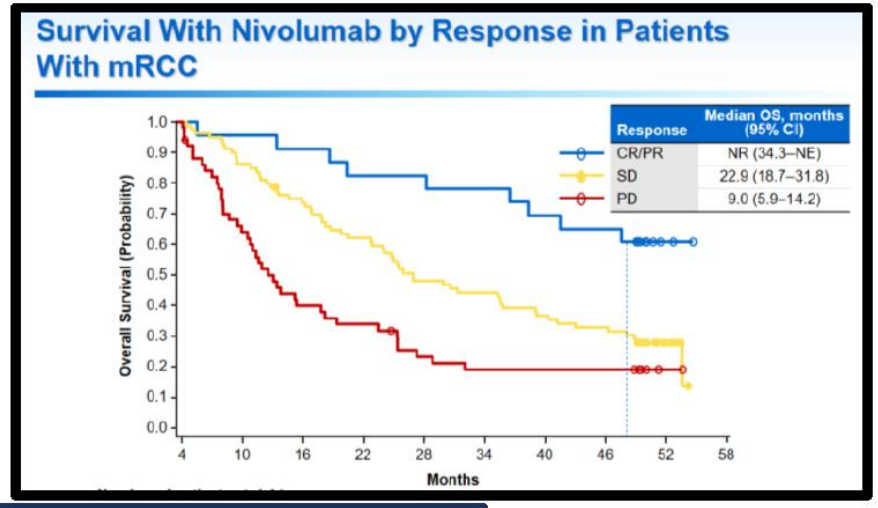
Dako PD-L1 IHC 28-8 pharmDx test	Positive tumor cells		Ipi + Nivo vs Sun
Baseline PD-L1 expression			
<1%	93/284	114/278	0.73 (0.56–0.96)
≥1%	28/100	57/114	0.45 (0.29–0.71)
Not reported	19/41	17/30	0.75 (0.39–1.45)

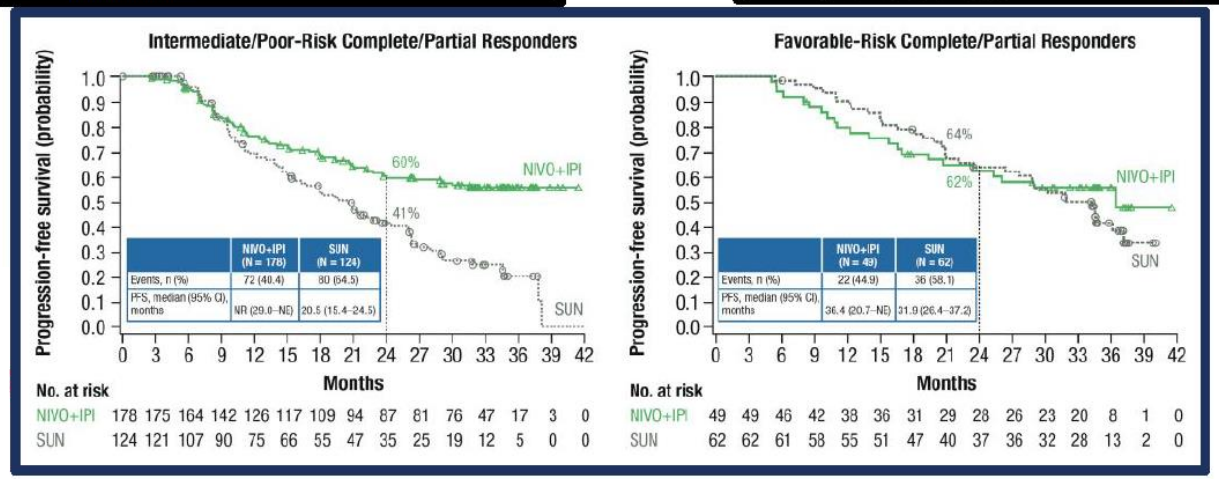
COMPLETE RESPONSES



COMPLETE RESPONSES





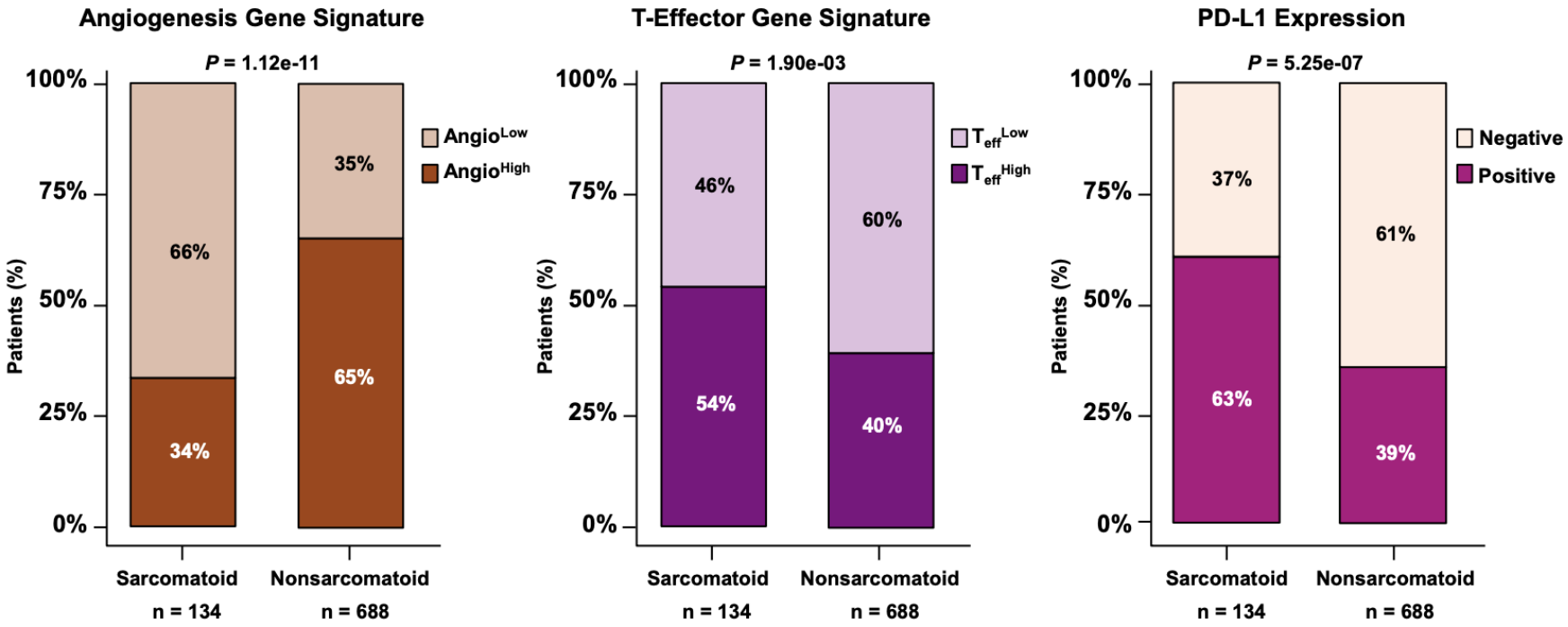


Grünwald V, Eur Urol 2015; McDermott D, ASCO 2016; Tannir N, et al. ASCO GU

- ✓ **Associated with OS**
- ✓ **Opportunity of treatment discontinuation**

SARCOMATOID COMPONENT

Lower Angiogenesis Gene Expression and Higher PD-L1 expression



Rini BI, et al. *Ann Oncol*. 2018;29(Suppl 8): Abstract LBA31.

SARCOMATOID COMPONENT

	IPILIMUMAB + NIVOLUMAB int/poor		PEMBROLIZUMAB + AXITINIB	
	ALL COHORT	SARCOMATOID	ALL COHORT	SARCOMATOID
N	425	60	432	51
ORR, %	42%	57%	59%	59%
CR, %	11%	18%	6%	13%
PFS, mos	11.6	8.4	15.1	NR
1-year OS	80%	73%	89.9%	NA

- Retrospective analysis.

- No central pathology review.

- Unknown extent of sarcomatoid dedifferentiation.

OUTLINE

1. Current first line management in advanced renal cell carcinoma

2. How to select patients for 1st line treatment ?

3. Subsequent therapies

4. Future perspectives for 1st line treatment

SUBSEQUENT THERAPY

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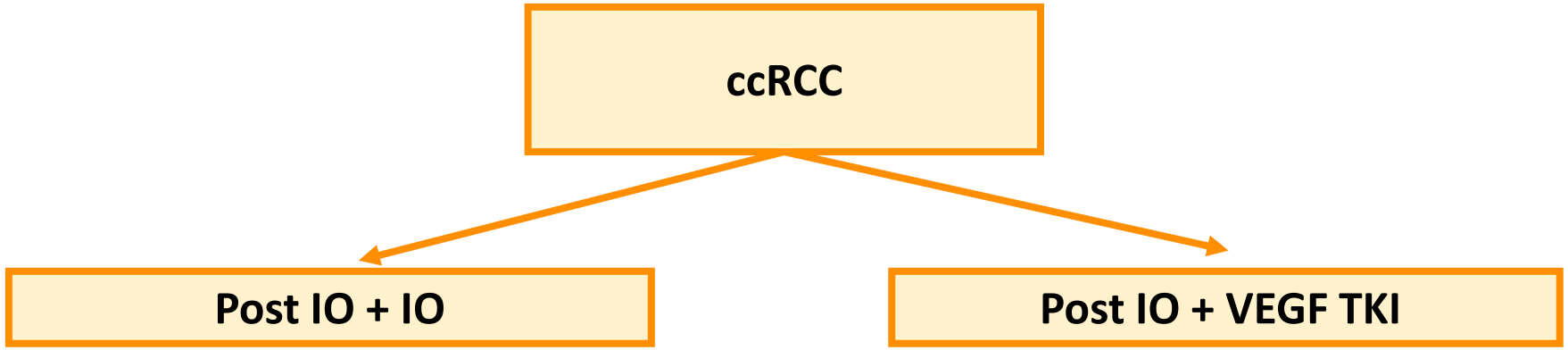
- Only retrospective data in the post IO first line setting:

Study	Agents	N	ORR	PFS/TTF
Retrospective	VEGF TKI/mTOR (axi/eve++)	56	13%	6.6 mo
Retrospective	VEGF TKI	70	28%	6.4 mo
Retrospective	VEGF TKIs (cabo/axi)	56	33%	8 mo
Retrospective	Cabozantinib	86	36%	6.6 mo
Phase 2	Axitinib, dose titrated	38	38%	9.2 mo
Retrospective	TKIs (post combo nivo/ipi)	33	36%	8 mo
Retrospective	TKIs	70	41%	13.2 mo

Unknown what is the impact of frontline combination on subsequent treatment activity

SUBSEQUENT THERAPY



Any VEGF TKI can be used

VEFG TKI remains active after VEGF failure

Cabozantinib is the more selective TKI and probably the most active

ORR: 36%, ORR + SD: 79%

OUTLINE

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1. First line current management in RCC

2. How to select patients for 1st line treatment ?

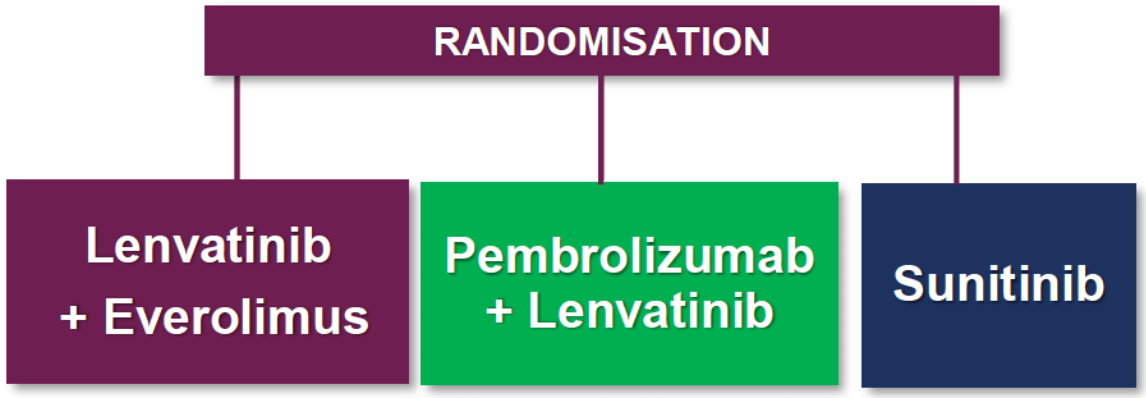
3. Subsequent therapies

4. Future perspectives for 1st line treatment

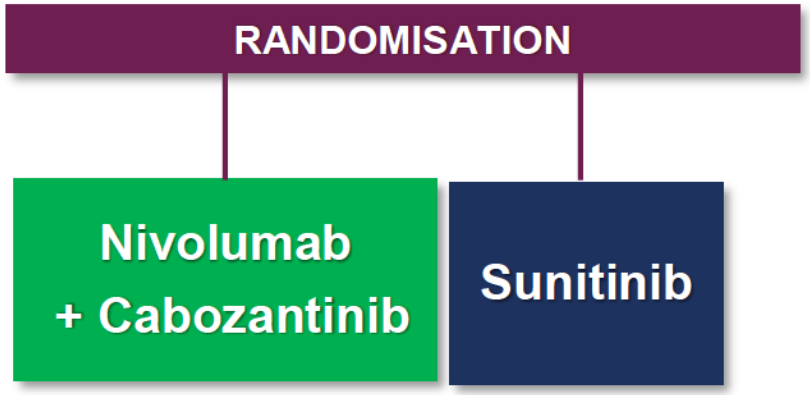
PERSPECTIVES

1. Evaluate other VEGF TKI combinations in frontline setting

Phase III N=1069
Primary endpoint: PFS,OS



Phase III N= 638
Primary endpoint: PFS



PERSPECTIVES

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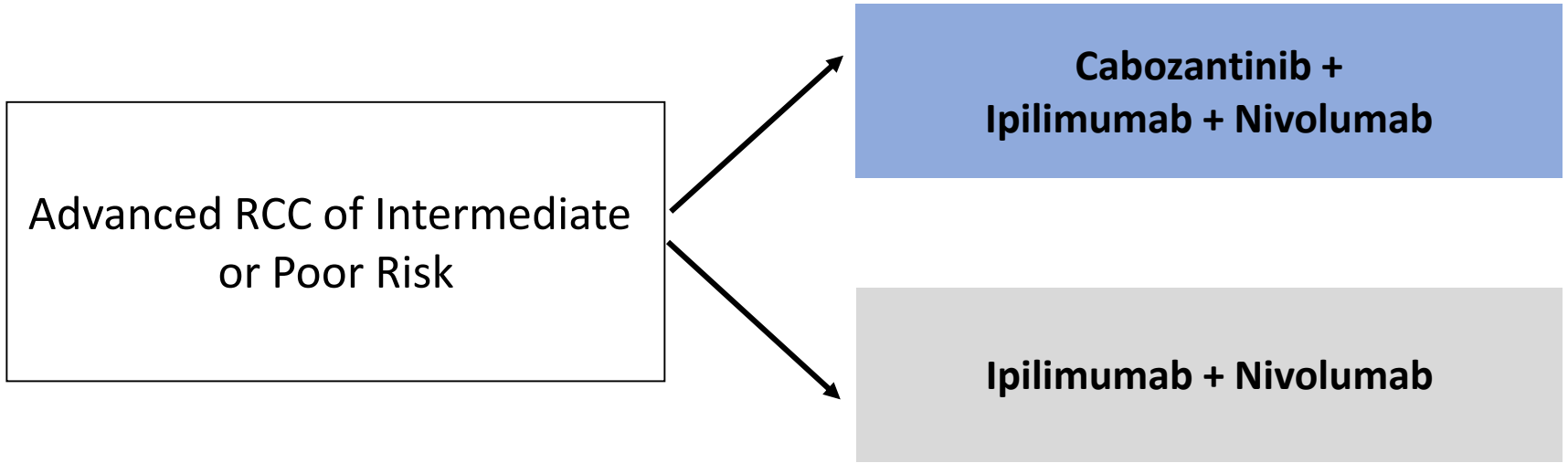
2. Evaluate other IO combinations comparing with the new SOC in front line setting

COSMIC-313 STUDY



PERSPECTIVES

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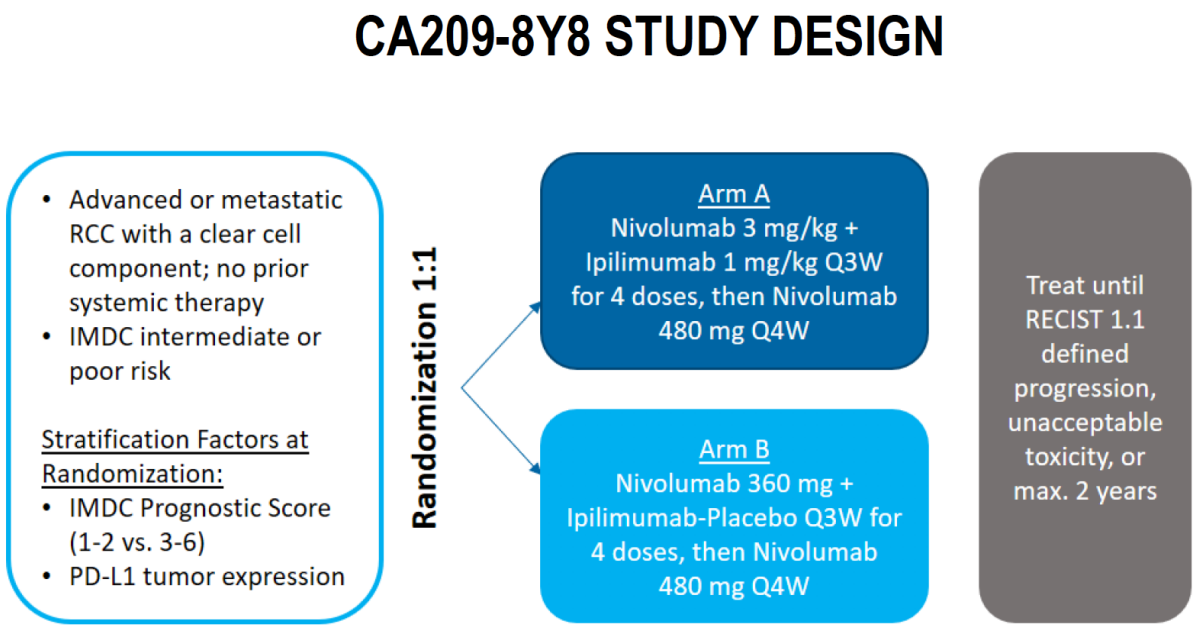
3. Evaluate Monotherapy versus Combination

- Some data available for IO monotherapy in the 1st line setting

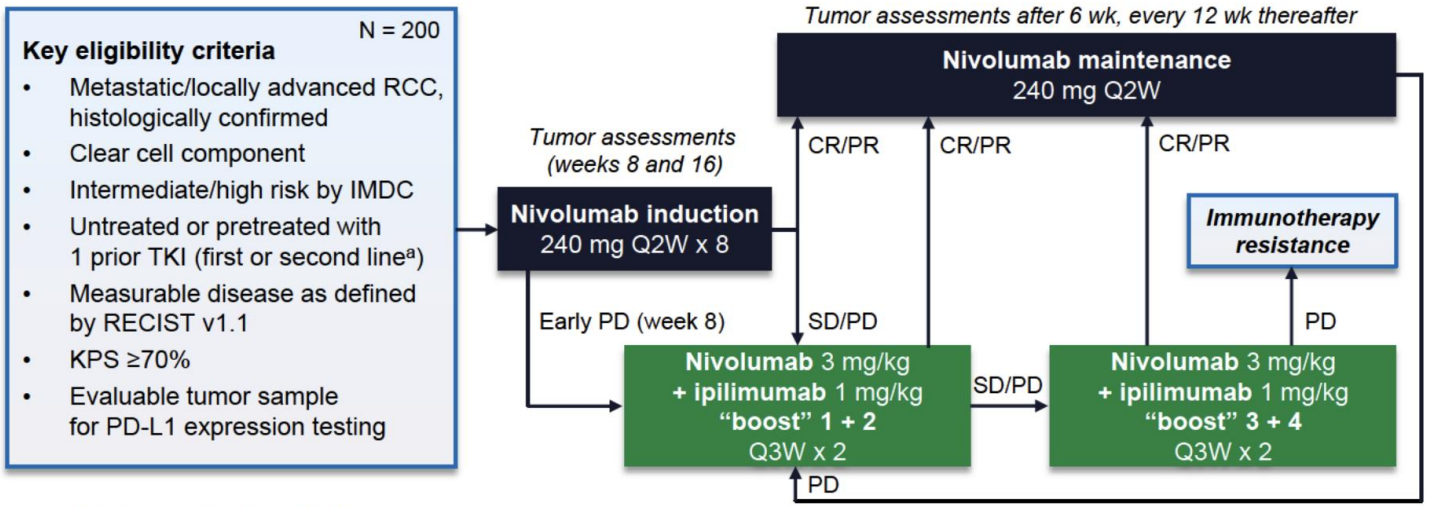
  - Pembrolizumab (n=110) - ORR 38% (CR: 3%)

  - Phase 3 comparing Ipi-Nivo versus Nivo in the 1st line setting (NCT03873402)



PERSPECTIVES

4. Evaluate Sequence versus Combination



- **Primary endpoint:** ORR
- **Secondary endpoints:** PFS, OS, RR after nivo + ipi "boosts", safety (TRAE), QoL (FKSI-19)

	1L (n=108) N_{alone} ORR#	1L (n=108) N ± N+I BOR†
ORR (BOR), n (%)	**31** (28.7)	**40** (37.0)
Complete response, n (%)	**2** (1.9)	**2** (1.9)
Partial response, n (%)	**29** (26.9)	**38** (35.2)
Stable disease, n (%)	**26** (24.1)	**26** (24.1)
Progressive disease, n (%)	**13** (12.0)	**38** (35.2)
Early Progressive disease / 'Boost' Week 8, n (%)	**22** (20.4)	
Not evaluable *, n (%)	**16** (14.8)	**4** (3.7)

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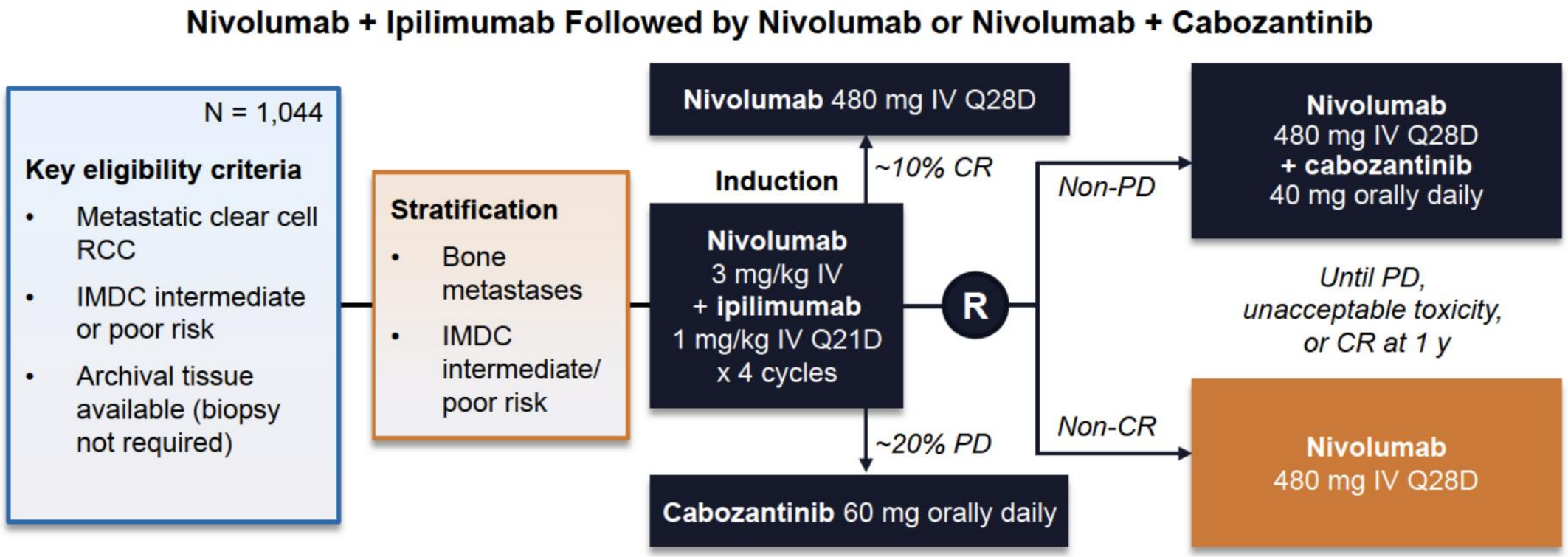
4. Evaluate Sequence versus Combination



- **Primary endpoint:** OS
- **Key secondary endpoints:** PFS, 1-y CR rate, ORR by RECIST, toxicity, and correlatives

CONCLUSIONS

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- **CPI in combination is the current SOC in 1st line therapy -** The addition of ipilimumab or axitinib is the key decision
- **IMDC prognostic score need to be used in decision making -** Biology appears to be different in good vs. intermediate / poor risk
- **New combinations are under investigation -** OS benefit is the gold standard
- **Not predictive biomarkers are available**
- **There is a lack of data on treatment after 1st line -** VEGF TKI not used previously is justified

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THANK YOU FOR YOUR ATTENTION

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