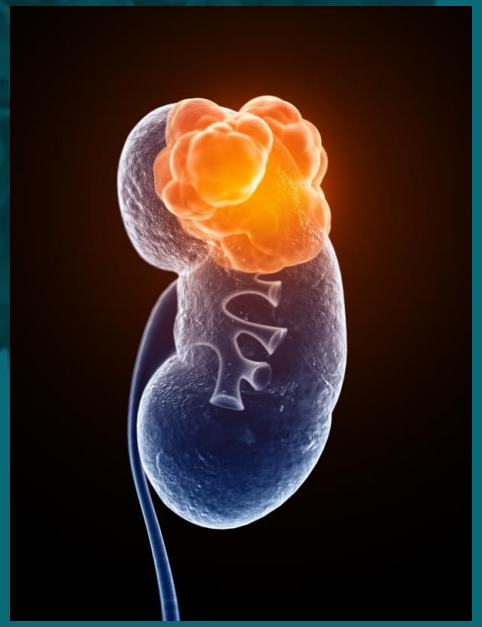
BMUC
UROLOGY - RADIATION ONCOLOGY - MEDICAL ONCOLOGY

11th Belgian Multidisciplinary Meeting on Urological Cancers

SYSTEMIC TREATMENT CHOICES IN RCC: WHO NEEDS WHAT ?

15/03/2024

Pr. Christine Gennigens
MD, PhD
Medical Oncology Department



INSTITUT DE CANCÉROLOGIE ARSÈNE BURNY
CHU de Liège

LIÈGE université
Médecine

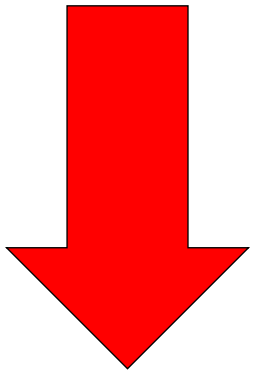
FINANCIAL DISCLOSURE

SPEAKER'S FEE	BMS; Ipsen; GSK; MSD
GRANTS	AstraZeneca; Pharmamar; Roche
BOARDS	Astra Zeneca; BMS; Esaï; GSK; MSD; Pfizer
CONSULTANCE	GSK; MSD; Deciphera
TRAVELS	Ipsen; GSK; Pfizer; MSD; AstraZeneca

FIRST-LINE METASTATIC DISEASE

SHOULD WE TREAT « ALL » THE METASTATIC PATIENTS ???

LIMITED DISEASE BURDEN AND ASYMPTOMATIC



- **Close active surveillance !!!**
- **Initiation of systemic therapy at onset of new lesions, accelerated growth of existing lesions, or symptomatic disease**

IF "OLIGO-METASTATIC" DISEASE

Tkink about LOCAL TREATMENTS !!!

SURGERY

RADIOSURGERY

RADIOFREQUENCE

- Prolonging survival
- Avoiding systemic treatments if complete resection

PHASE III-RANDOMIZED CONTROLLED TRIALS-RESULTS

LANDSCAPE HAS CHANGED CONSIDERABLY

PHASE 3 RCTs

IO + IO

CHECKMATE 214

IO + TKI

KEYNOTE-426

CHECKMATE 9R

CLEAR

~~JAVELIN RENAL 101~~

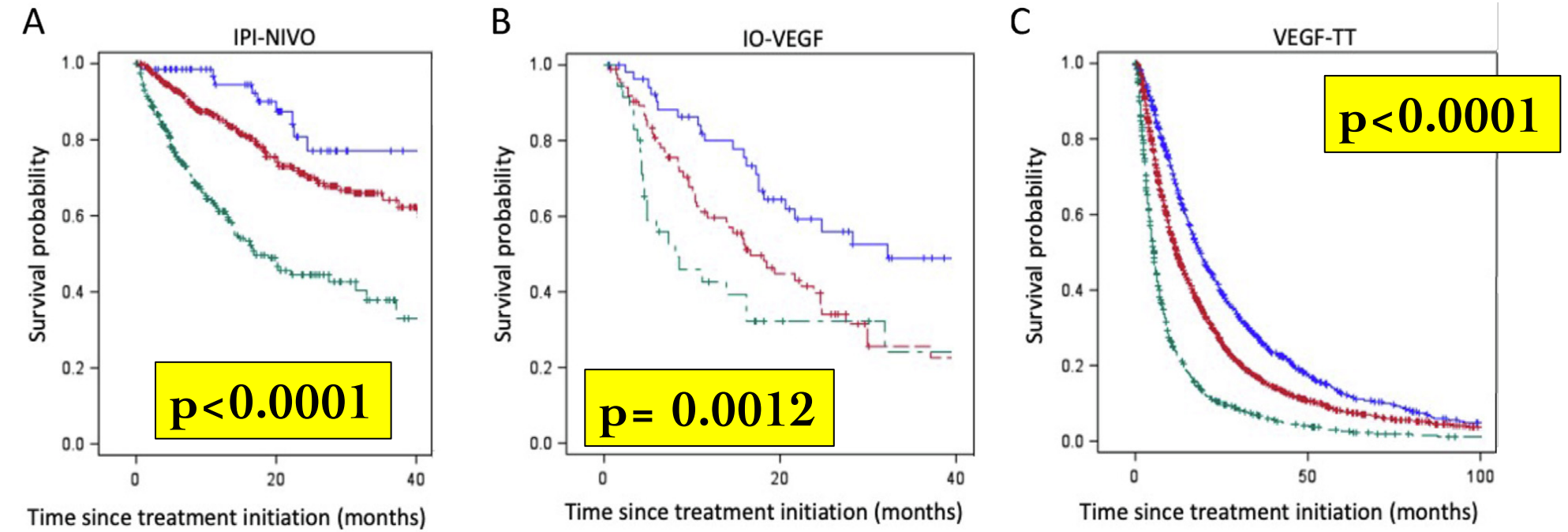
~~IMMOTION 151~~

- Benefit in PFS but not in OS
- Anti-PDL1 ?

Outcomes for International Metastatic Renal Cell Carcinoma Database Consortium Prognostic Groups in Contemporary First-line Combination Therapies for Metastatic Renal Cell Carcinoma

Matthew S. Ernst[a], Vishal Navani[a], J. Connor Wells[a], Frede Donskov[b], Naveen Basappa[c], Chris Labaki[d], Sumanta K. Pal[e], Luis Meza[e], Lori A. Wood[f], D. Scott Ernst[g], Bernadett Szabados[h], Rana R. McKay[i], Francis Parnis[j], Cristina Suarez[k], Takeshi Yuasa[l], Aly-Khan Lalani[m], Ajjai Alva[n], Georg A. Bjarnason[o], Toni K. Choueiri[d], Daniel Y.C. Heng[a,]*

European Urology 2023



IMDC scores continue to predict clinical outcomes in the era of ICI-based combinations

CHECKMATE 214 TRIAL

1096pts

mFU = 99 mths

- Coprimary end points = OS, ORR, and PFS among patients with intermediate or poor prognostic risk

Patients

- **Treatment-naïve advanced or metastatic clear-cell RCC**
- **Measurable disease**
- **KPS ≥70%**
- **Tumor tissue available for PD-L1 testing**

Randomize 1:1

Stratified by
- IMDC prognostic score (0 vs 1–2 vs 3–6)
- Region (US vs Canada/Europe vs Rest of World)

Treatment

Arm A
3 mg/kg nivolumab IV + 1 mg/kg ipilimumab IV Q3W for four doses, then 3 mg/kg nivolumab IV Q2W

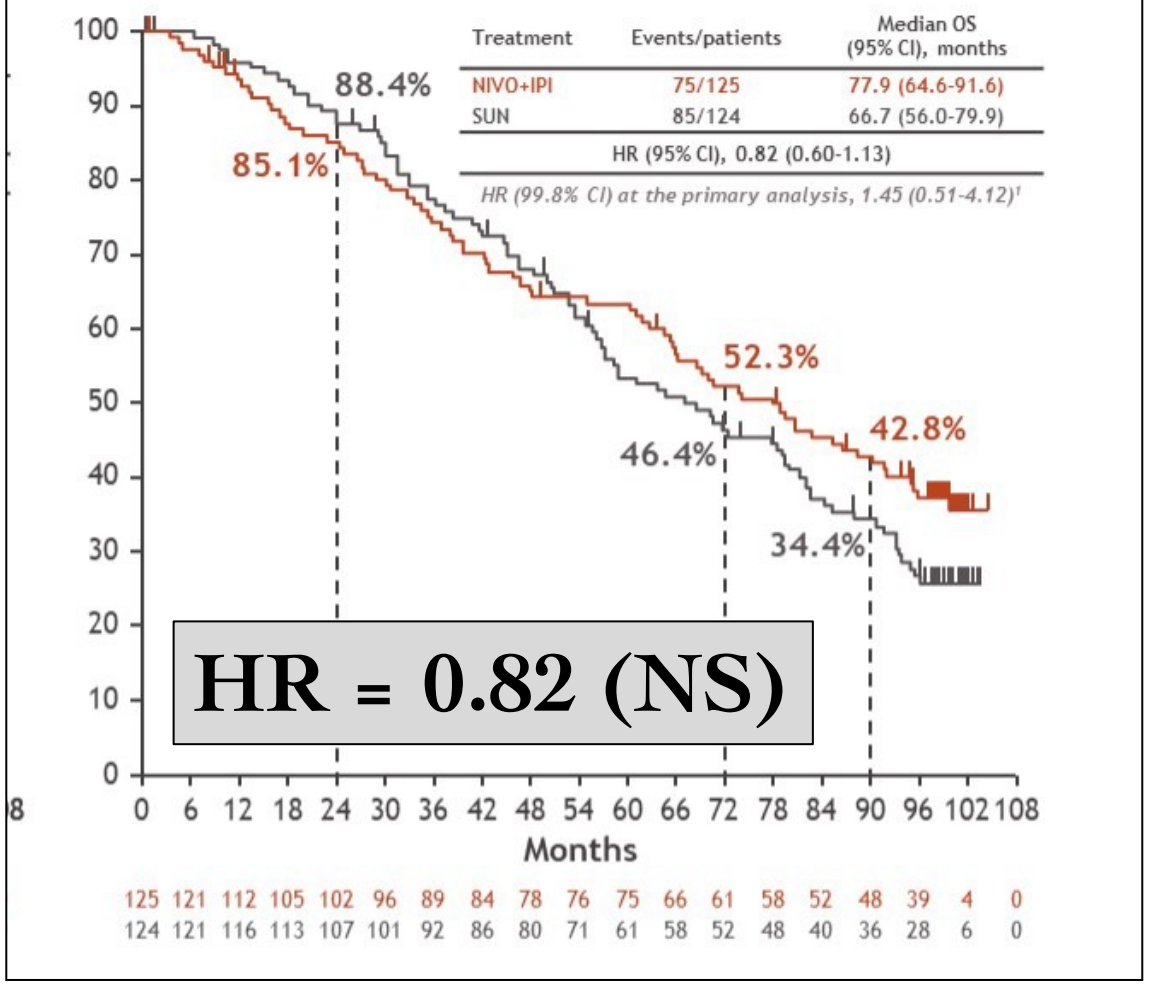
Arm B
50 mg sunitinib orally once daily for 4 weeks (6-week cycles)

Treatment until progression or unacceptable toxicity

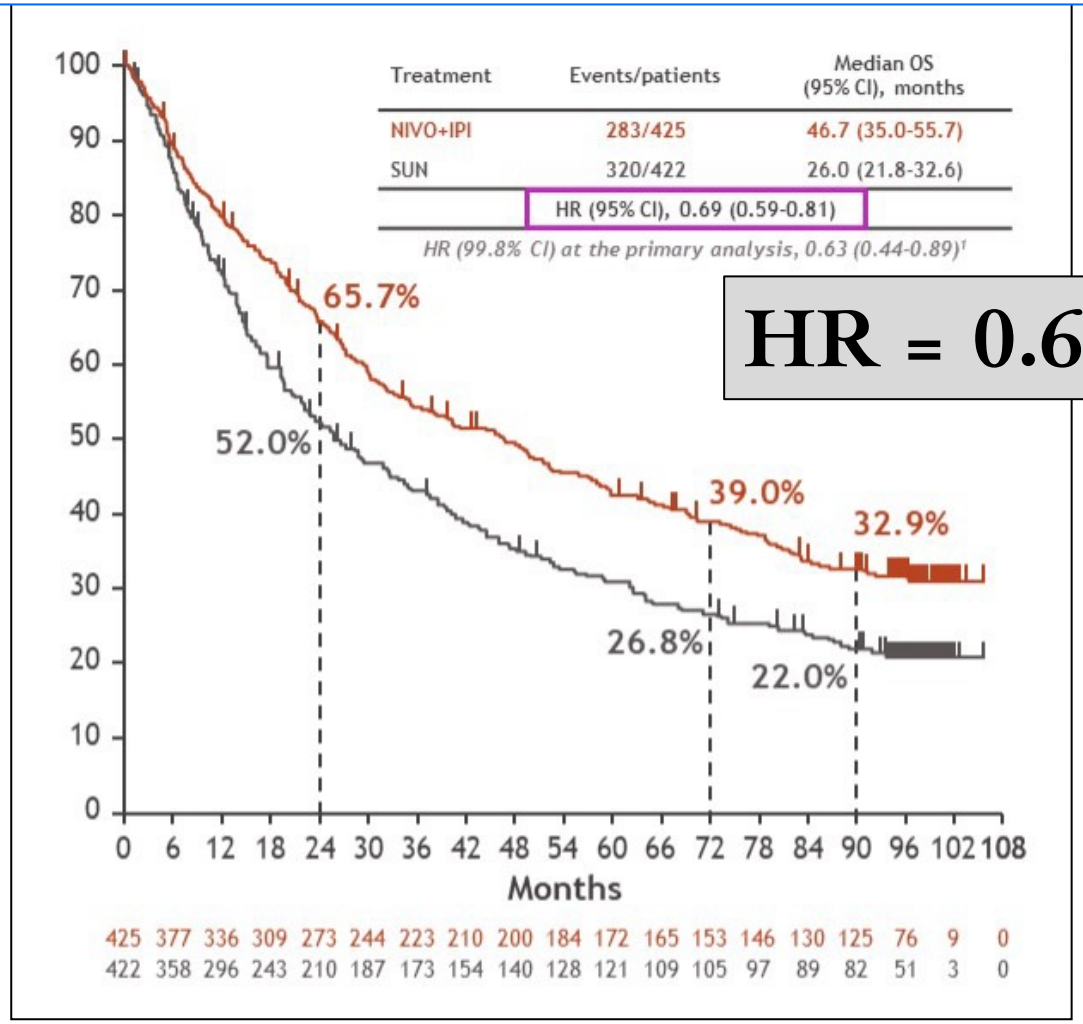
FAVO/INTERM./POOR = 23% / 61% / 17%

OVERALL SURVIVAL (OS)

FAVORABLE



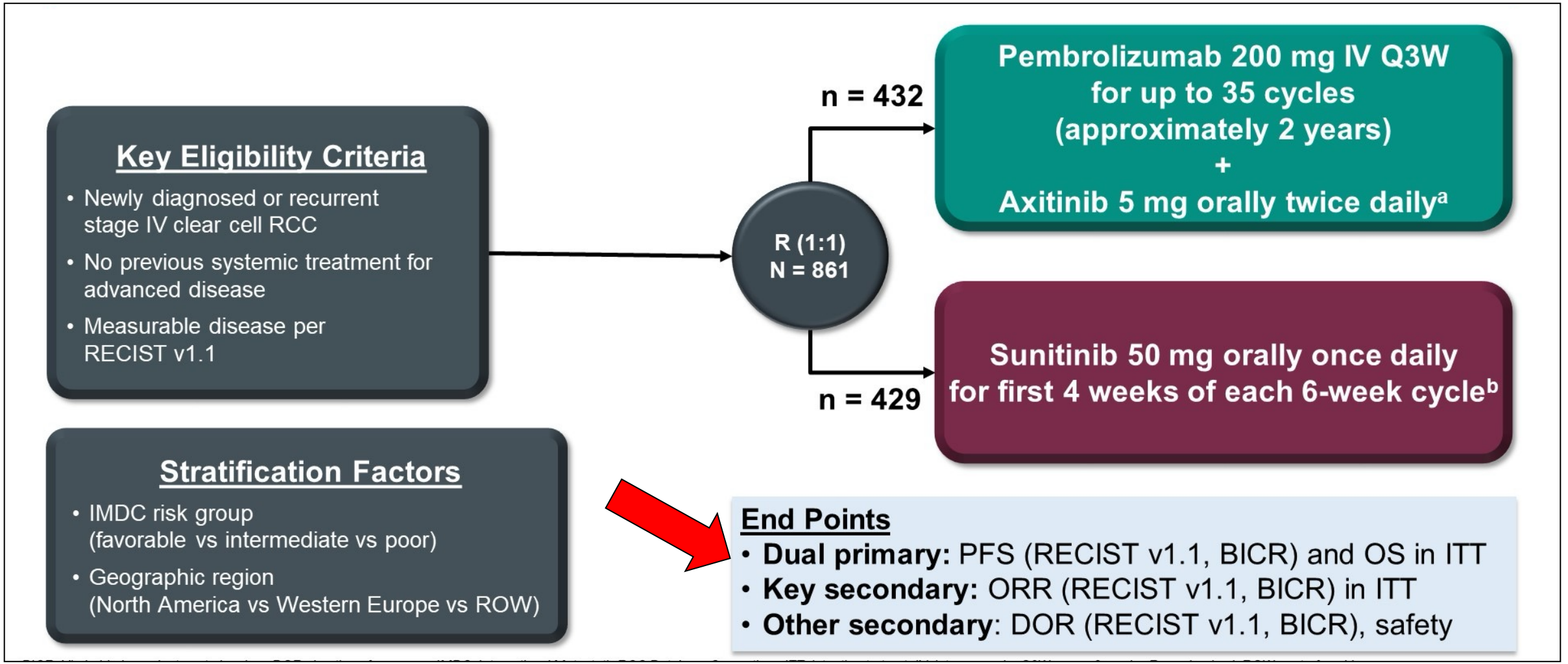
INTERMEDIATE/POOR



KEYNOTE-426 TRIAL

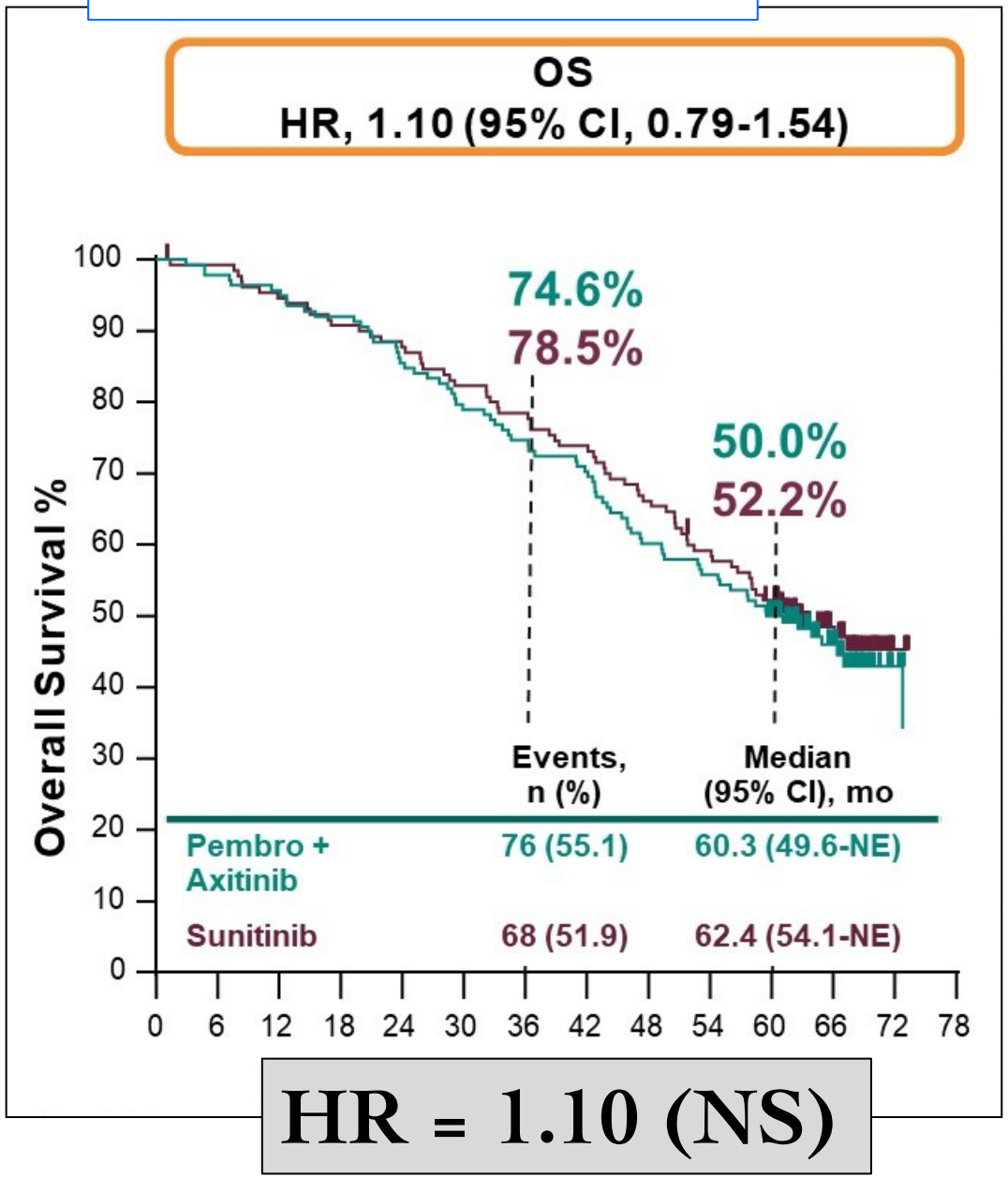
861 pts

mFU = 67 mths



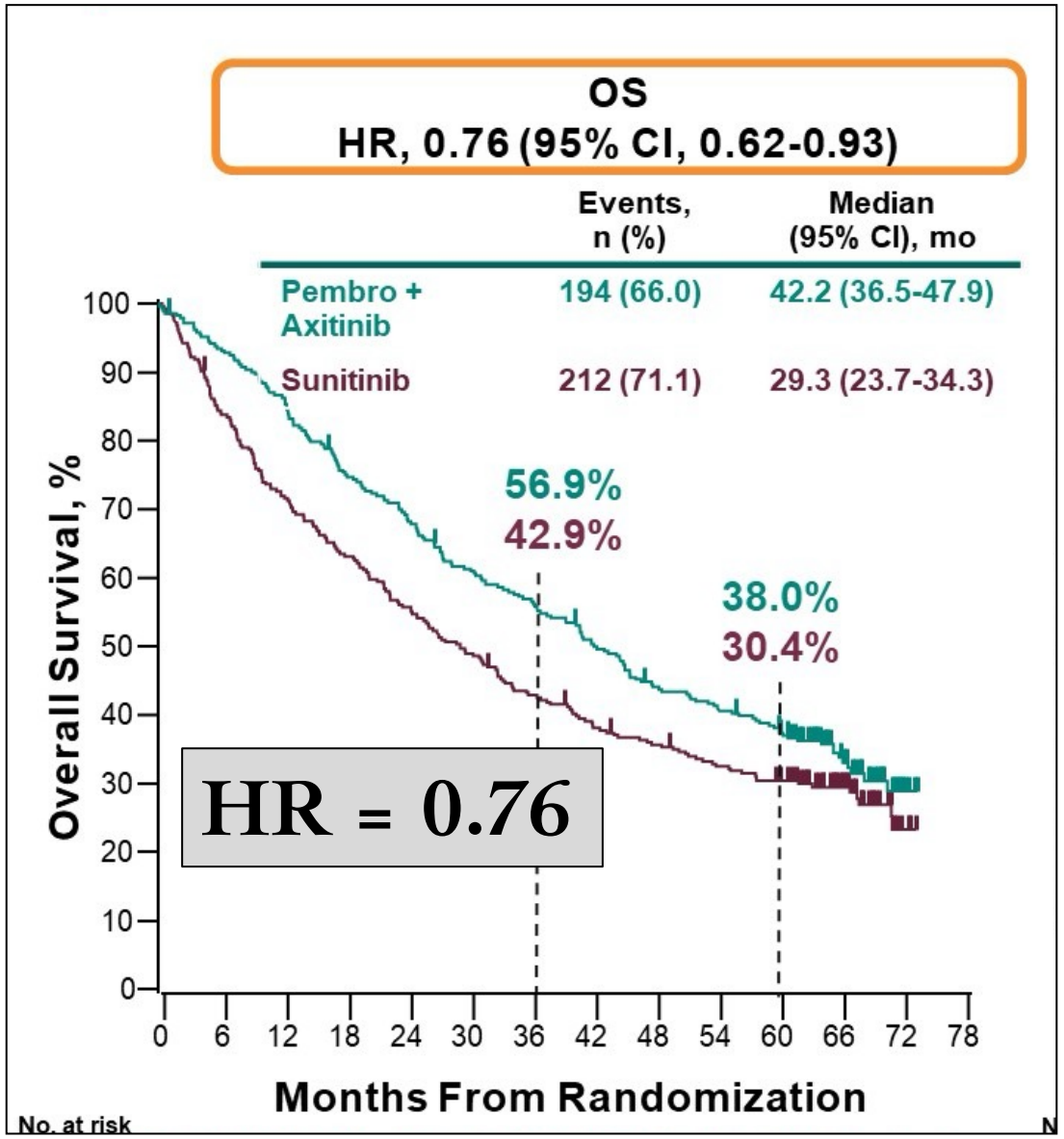
FAVO/INTERM./POOR = 32% / 55% / 13%

FAVORABLE



HR = 1.10 (NS)

INTERMEDIATE/POOR



CHECKMATE-9ER TRIAL | 651 pts | mFU= 55 mths

Patients (N=651)

- Previously untreated advanced or metastatic RCC
- Clear cell component
- Any IMDC risk group

Stratification factors:

- IMDC risk score
- Tumor PD-L1 expression*
- Geographic region

R 1:1

Cabo 40 mg PO QD
+ Nivo 240 mg IV Q2W

SUN 50 mg PO QD, cycle of 4 weeks on/ 2 weeks off

Treat until RECIST v1.1-defined progression or unacceptable toxicity†

Primary endpoint:

- PFS per BICR (RECIST v1.1)

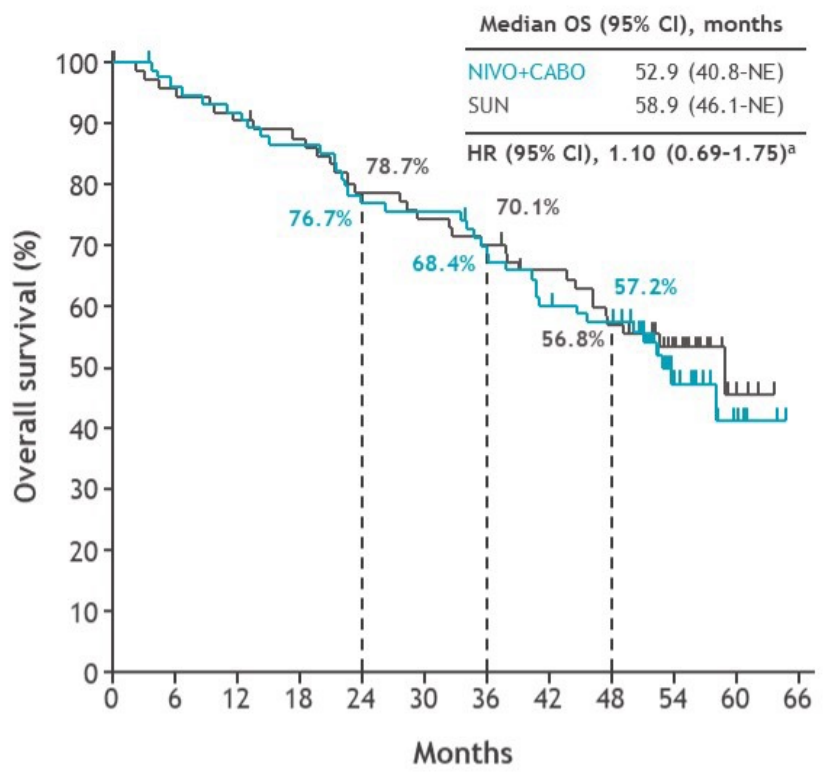
Secondary endpoints:

- OS
- ORR per BICR (RECIST v1.1)
- Safety

FAVO/INTERM./POOR = 23% / 58 % / 19%

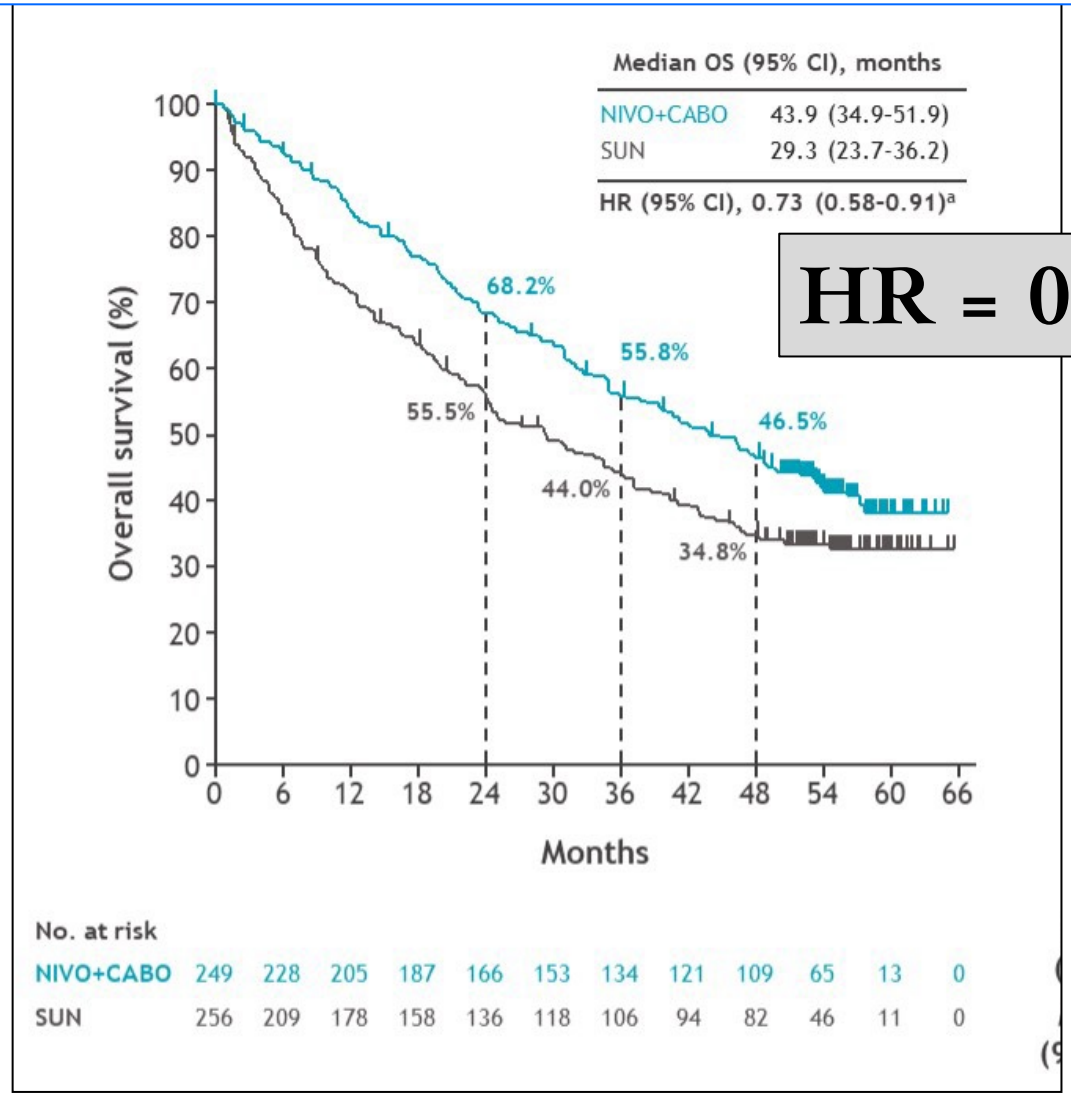
OVERALL SURVIVAL (OS)

FAVORABLE



HR = 1.10 (NS)

INTERMEDIATE/POOR

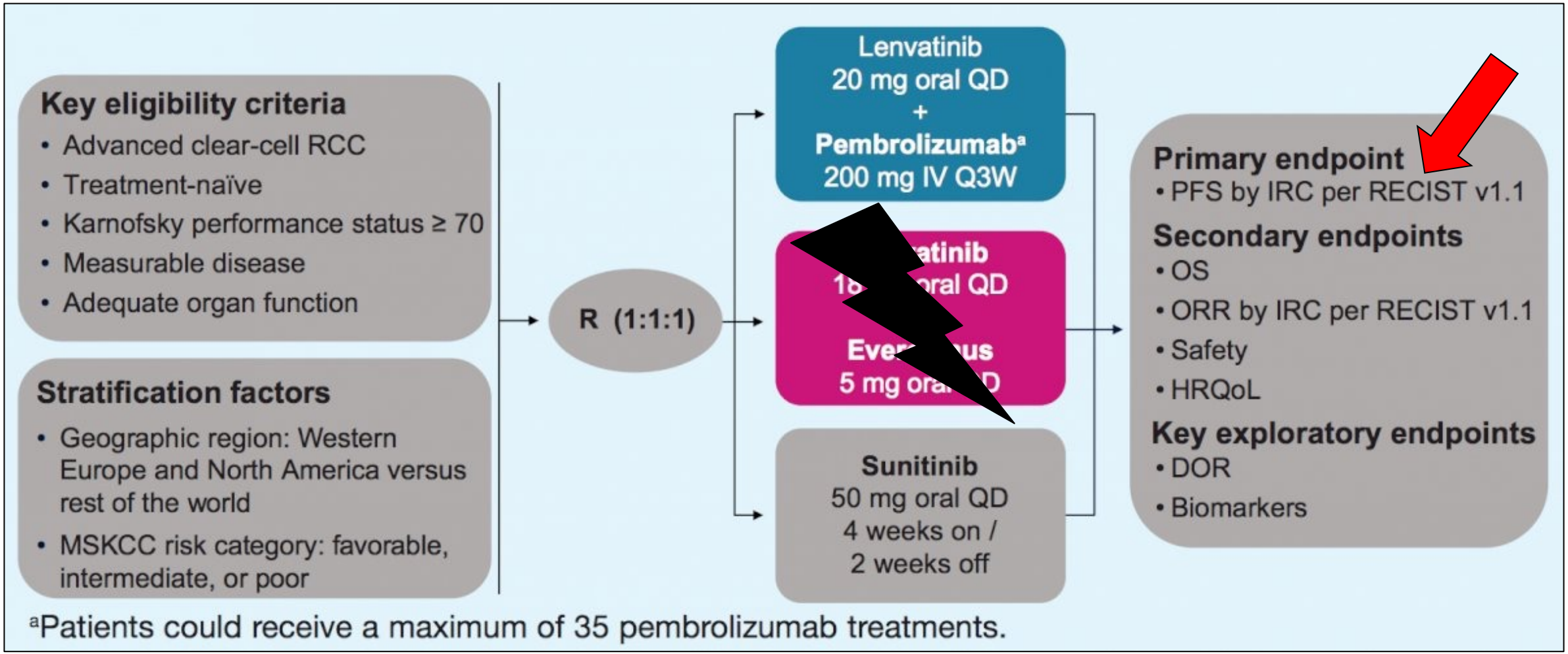


HR = 0.73

CLEAR TRIAL

712 pts

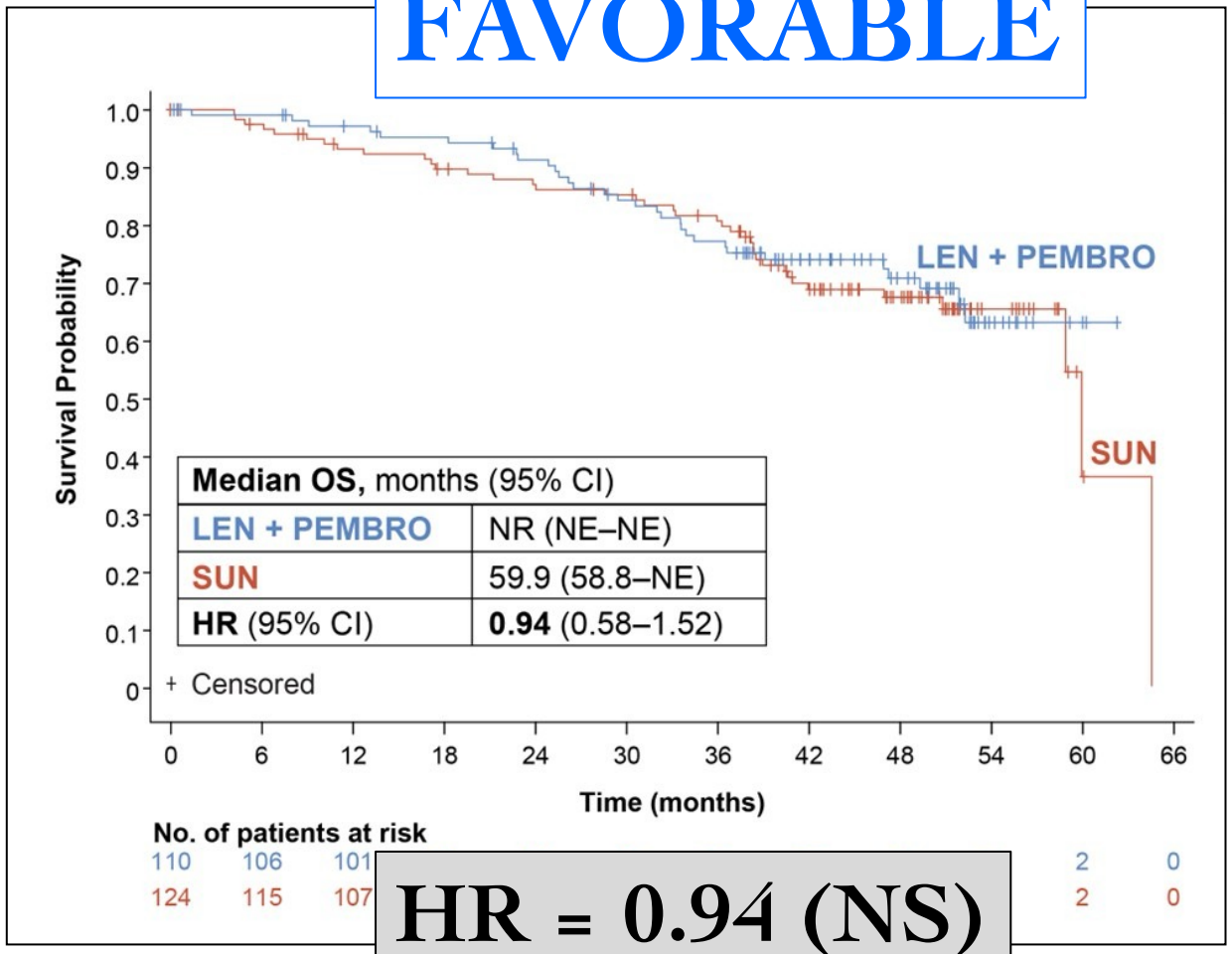
mFU= 49.8 mths



FAVO/INTERM./POOR = 32% / 59 % / 9%

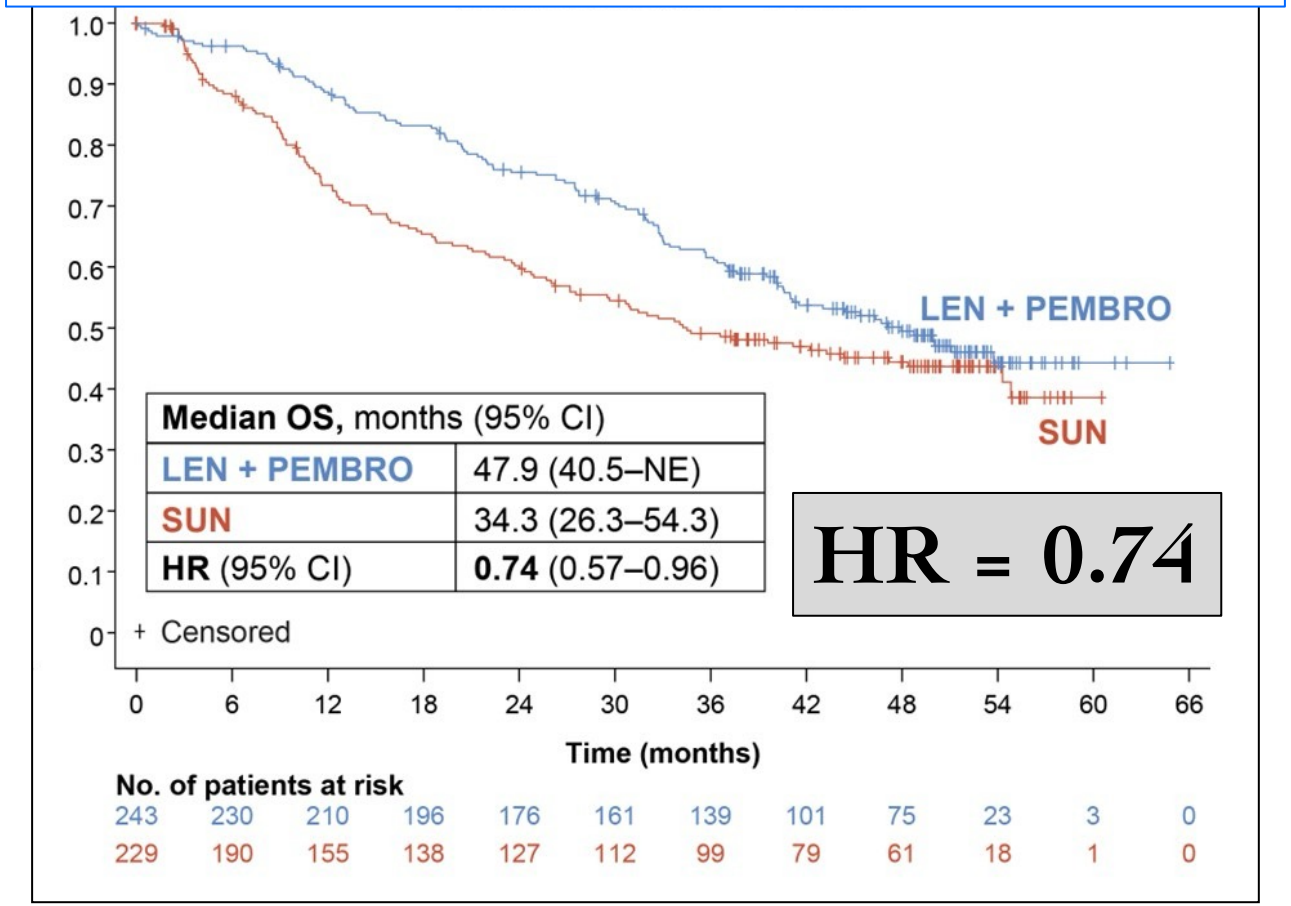
OVERALL SURVIVAL (OS)

FAVORABLE



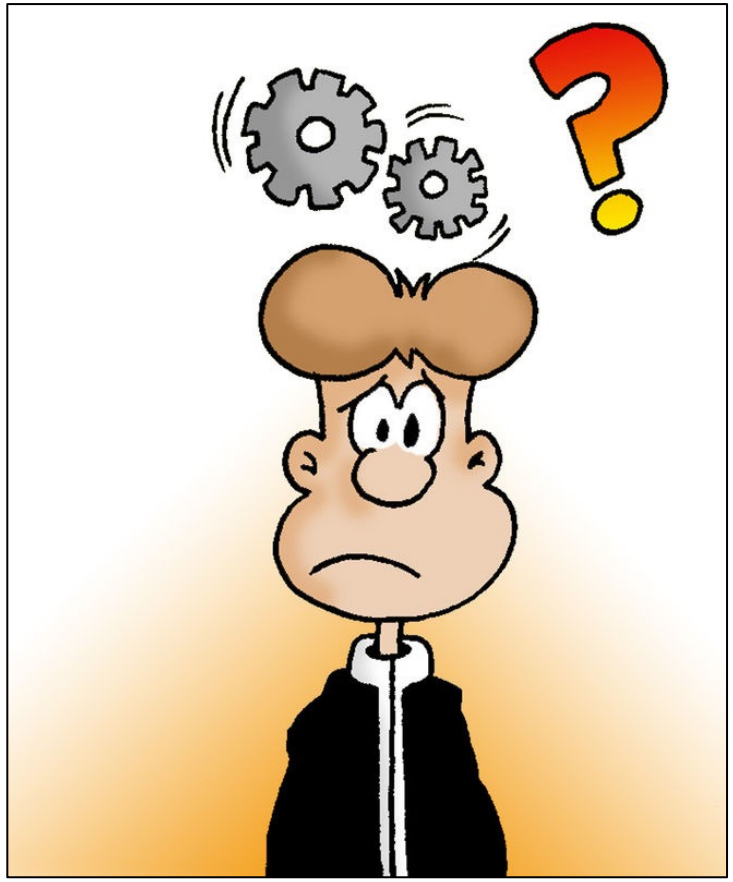
HR = 0.94 (NS)

INTERMEDIATE/POOR



HR = 0.74

WHAT IS THE « BEST FIRST SHOT » ???



NO HEAD TO HEAD (PROSPECTIVE) DATA EXIST

1 Which combination is the best ?
IO + IO or IO + TKI

2 If an IO + TKI combination is the choice, which TKI is the best?

HEAD-TO-HEAD COMPARISONS

PROSPECTIVE DATA

NOTHING

RETROSPECTIVE DATA

Zarrabi et al., ASCO 2021, Abstract 4535

Chun Loo Gan et al., ASCO GU 2021, Abstract 276

Wick-Gennigens et al., BSMO 2024 Abstract

NO STATISTICALLY DIFFERENCE

2L THERAPY

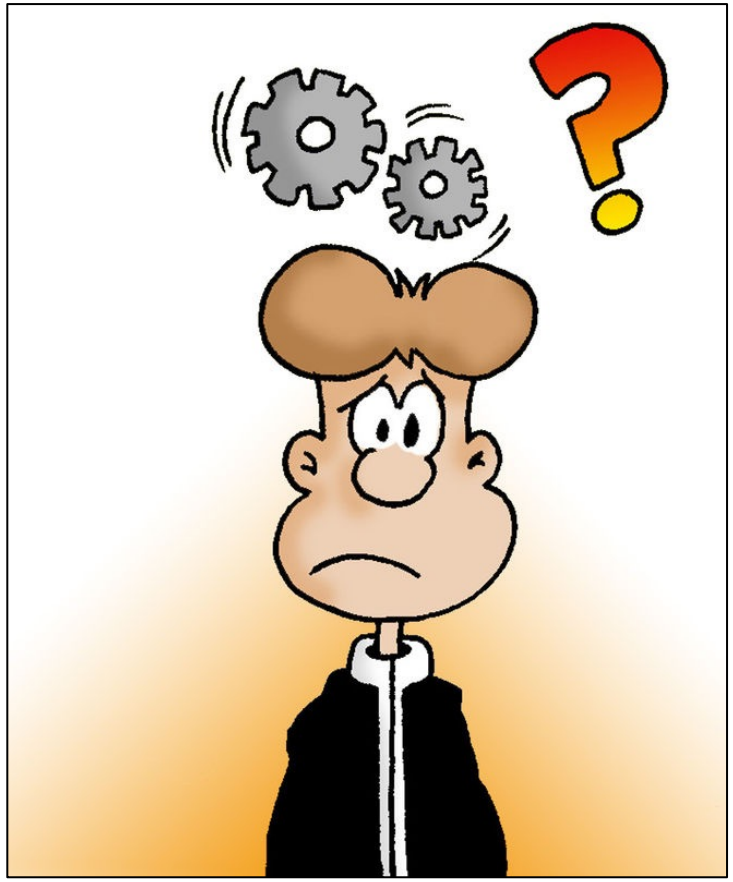
35-58%

1L therapy	Centre type	Sample size	Patients receiving 2L therapy
AxiPem, IpiNivo or TKI monotherapy[1]	Community	1,538	35%
IpiNivo or AxiPem[2]	Specialist	99	37–53%
IpiNivo[3]	Specialist	704	58%

Not all patients (35-58%) will receive 2L therapy, highlighting the importance of choosing the best treatment first

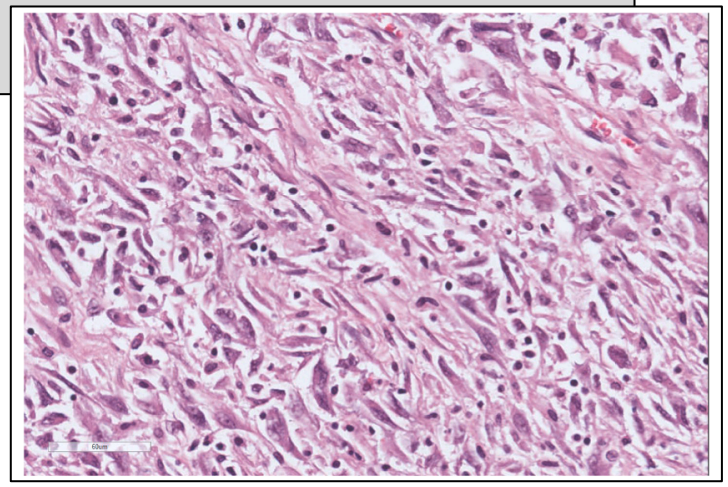
Daniel Heng, Ipsen satellite symposium, ESMO 2023

WHAT IS THE BEST CANDIDATE FOR IO+IO ???



1

Particularly relevant with sarcomatoïd component…



MOLECULAR SUBTYPE CHARACTERISTICS

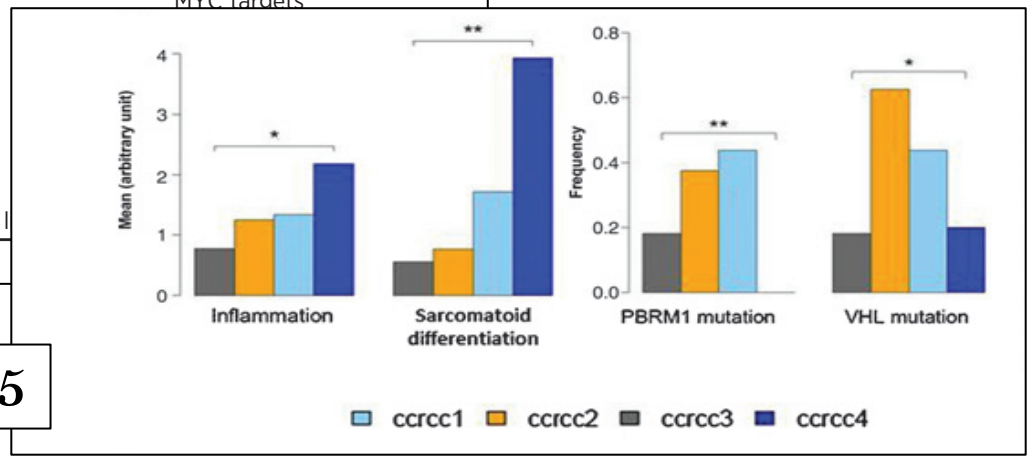
Subgroup (frequency)	ccrcc1 (33%)	ccrcc2 (41%)	ccrcc3 (11%)	ccrcc4 (15%)
Outcome under sunitinib				
Early PD	22.22%	2.78%	0.00%	26.67%
PR	40.74%	52.78%	70.00%	20.00%
Median OS (month)	24	35	50	14
Median PFS (month)	13	19		8
Clinical characteristics				
IMDC				
Good prognosis	6%	21%	18%	7%
Intermediate prognosis	69%	60%	64%	60%
Poor prognosis	25%	18%	18%	33%
MSKCC				
Good prognosis	10%	24%	27%	0%
Intermediate prognosis	58%	50%	63%	93%
Poor prognosis	32%	26%	9%	7%
Molecular characteristics				
Pathology characteristics				
Mean inflammation intensity (scale 0–3)	1.3	1.2	0.8	2.2
Mean sarcomatoid differentiation (%)	7.5	3.7	1.7	24.6
Mutations				
VHL	46.67%	62.50%	20.00%	20.00%
PBRM1	46.67%	37.50%	20.00%	0.00%
Upregulated pathways	MYC targets Glycolysis Hypoxia	Glycolysis Hypoxia		Immunity Apoptosis Chemotaxis MYC targets
MYC expression level	++	+	–	
Methylation status	Hypermethylated +			
Polycomb stem-cell phenotype	++		–	
Copy number amplification				
Proposal for names	MYC.UP	Classical	Normal l	

NORMAL-LIKE

IMMUNE-HIGH

IMMUNE-LOW

ANGIO-HIGH



Beuselinck et al., 2015

EFFICACY OUTCOMES / SARCOMATOID DEDIFFERENTIATION

	CM 214[47]		KN-426[65]		JAVELIN Renal 101[66]		CM 9ER[67]		CLEAR[68]	
Therapies	Nivo/Ipi	Sun	Pembro/Axi	Sun	Avelumab/Axi	Sun	Nivo/Cabo	Sun	Len/Pem	Sun
Median OS (m)	NR	14.2	–	–	–	–	NR	19.7	NR	NR
OS HR	0.45		0.58		0.78		0.36		0.91	
(95% CI)	(0.30–0.70)		(0.21–1.59)		(0.36–1.72)		(0.16–0.82)		(0.32–2.58)	
Median PFS (m)	26.5	5.1	NR	8.4	7.0	4.0	10.9	4.2	11.1	5.5
PFS HR	0.54		0.54		0.57		0.39		0.39	
(95% CI)	(0.33–0.86)		(0.29–1.00)		(0.32–1.00)		(0.22–0.70)		(0.18–0.84)	
ORR (%)	61	23	59	32	47	21	56	22	61	24
CR	19	3	12	0	4	0	9	2	-	-
PR	42	20	-	-	43	21	47	20	-	-
PD	20	23	-	-	15	36	12	34	-	-

CM 214 = CheckMate 214, KN-426 = KEYNOTE-426, CM 9ER = CheckMate 9ER, nivo = nivolumab, ipi = ipilimumab, sun = sunitinib, axi = axitinib, cabo = cabozantinib, len = lenvatinib, pem = pembrolizumab, OS = overall survival, *m* = months, NR = not reached, HR = hazard ratio, CI = confidence interval, ORR = objective response rate, CR = complete response, PR = partial response, PD = progressive disease.

Hahn et al., 2022

2 Cardiac contra-indication

HTA ANY GRADE / GRADE 3+

IPI + NIVO	2% / < 1%
AXI + PEMBRO	44% / 22%
CABO + NIVO	30% / 11%
LENVA + PEMBRO	56% / 29%

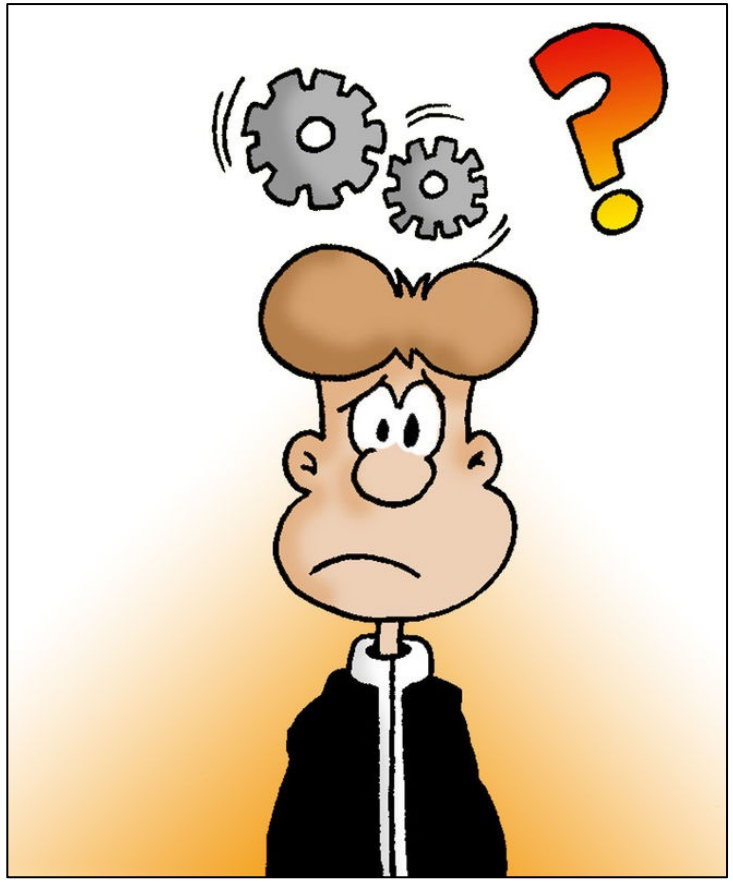
3

- Without rapid progression
- When the primary goal is CURE
- Only chance to use IPILIMUMAB

DURABLE »LATE« ENDPOINTS = OS

IPI + NIVO	mFU = 25 / 99 months	HR = 0.68 / 0.72
AXI + PEMBRO	mFU = 12 / 42 months	HR = 0.53 / 0.84
CABO + NIVO	mFU = 18 / 55 months	HR = 0.60 / 0.70
LENVA + PEMBRO	mFU = 27 / 49 months	HR = 0.72 / 0.79

WHAT IS THE BEST CANDIDATE FOR IO+TKI ???



1

Particularly relevant in anatomical sites where tumor growth may lead to adverse consequences (spinal canal; mediastinum;…)

2

- Particularly relevant in patients with
- aggressive disease
- high tumor burden and symptomatic patients
- with need rapid tumor shrinkage

PRIMARY PROGRESSIVE DISEASE (PD)

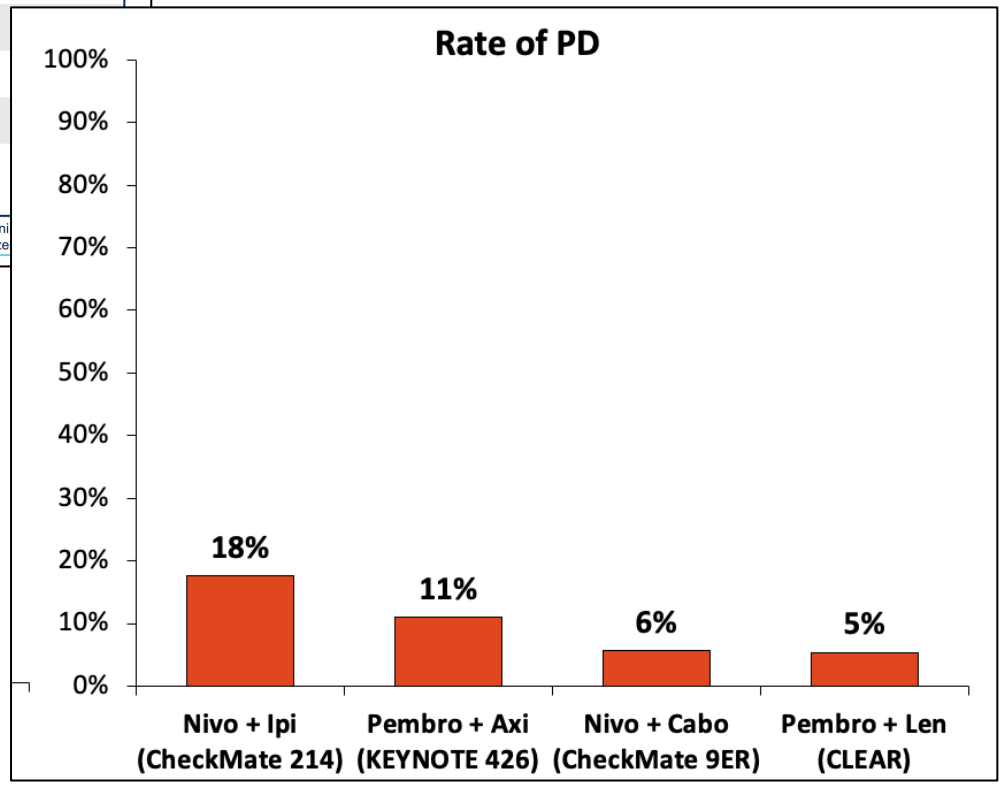
	Nivolumab + Ipilimumab CheckMate-214 n=1096	Pembrolizumab + Axitinib Keynote 426 n=861	Nivolumab + Cabozantinib CheckMate-9ER n=651	Pembrolizumab + Lenvatinib Clear n=1096
Follow-up, mo	48 (minimum)	42 (median)	18.1 (median)	26.6 (median)
Median PFS, mo	12.2	15.7	16.6	23.9
PFS HR	0.89	0.68	0.51	0.39
Median OS, mo	NR	45.7	NR	NR
OS HR	0.69	0.73	0.60	0.66
ORR, %	39.1	60.4	55.7	71.0
CR, %	10.7	10.0	8.0	16.1
PD, %	17.6	11.3	5.6	5.4
Median TTR, mo	--	2.8	2.8	1.9
Median DOR, mo	NR	23.6	20.2	25.8

Mo=months; PFS=Progression-free survival; HR=Hazard ratio; ORR=Objective response rate; CR=Complete response rate; PD=Progressive disease rate; TTR=Time to response; DOR=Duration of r... Albiges et al, ESMO Virtual Meeting, 2020; Rini... Meeting, 2021; Choueiri et al, NEJM, 2020; Motze...

High rate of early PD does not systematically reflect primary resistance (IO+IO)…

IO-IO = 18%

IO-TKI = 5-11%



OVERALL RESPONSE RATE (ORR)

	Intention-to-Treat Population						IMDC Risk Group					
							Favorable			Intermediate/Poor		
	mOS [HR (95% CI)]	mPFS [HR (95% CI)]	ORR (%)	Median DOR (Months)	CR (%)	Median TTR (Months)	mOS [HR (95% CI)]	mPFS [HR (95% CI)]	ORR (%)	mOS [HR (95% CI)]	mPFS [HR (95% CI)]	ORR (%)
Checkmate 214 # Ipi/Nivo vs. Sunitinib	56.0 vs. 38.0 [0.72 (0.62–0.85)]	12.0 vs. 12.0 [0.86 (0.73–1.01)]	39.12 vs. 32.3	NR vs. 25.0	10.7 vs. 2.6 *	2.8 vs. 4.0 *	74.0 vs. 68 [0. (0.65–	12.4 vs. 28.9	30.1	47.0 vs.	12.0 73 87)]	42.1 vs. 27.2
KEYNOTE 426 ## Pembro/Axi vs. Sunitinib	45.7 vs. 40.1 [0.73 (0.60–0.88)]	15.7 vs. 11.1 [0.68 (0.58–0.80)]	60.4 vs. 39.6	23.6 vs. 15.3	10.0 vs. 3.5	2.8 vs. 3.0	NR [(0.76–				8.2 81)]	56.5 vs. 34.9
CheckMate 9ER Nivo/Cabo vs. Sunitinib	NR vs. 29.5 [0.66 (0.50–0.87)]	17.0 vs. 8.3 [0.52 (0.43–0.64)]	54.8 vs. 28.4	20.2 vs. 11.5	9.3 vs. 4.3	2.8 vs. 4.5	NR vs. NR [0.94 (0.46–1.92)]	24.7 vs. 12.8 [0.58 (0.36–0.93)]	66.2 vs. 44.4	[0.74 (0.50–1.08)]	8.5 [0.58 (0.45–0.76)]	Int 55.9 vs. 28.7
										Poor NR vs. 11.2 [0.45 (0.27–0.76)]	Poor 9.9 vs. 4.2 [0.36 (0.23–0.56)]	Poor 37.7 vs. 10.3
CLEAR Pembro/ Lenvatinib vs. Sunitinib	NR vs. NR [0.66 (0.49–0.88)]	23.9 vs. 9.2 [0.39 (0.32–0.49)]	71.0 vs. 36.1	25.8 vs. 14.6	16.1 vs. 4.2	1.94 vs. 1.94	NR vs. NR [1.15 (0.55–2.40)]	28.1 vs. 12.9 [0.41 (0.28–0.62)]	68.2 vs. 50.8	NR vs. NR [0.58 (0.42–0.80)]	22.1 vs. 5.9 [0.36 (0.28–0.47)]	72.4 vs. 28.8

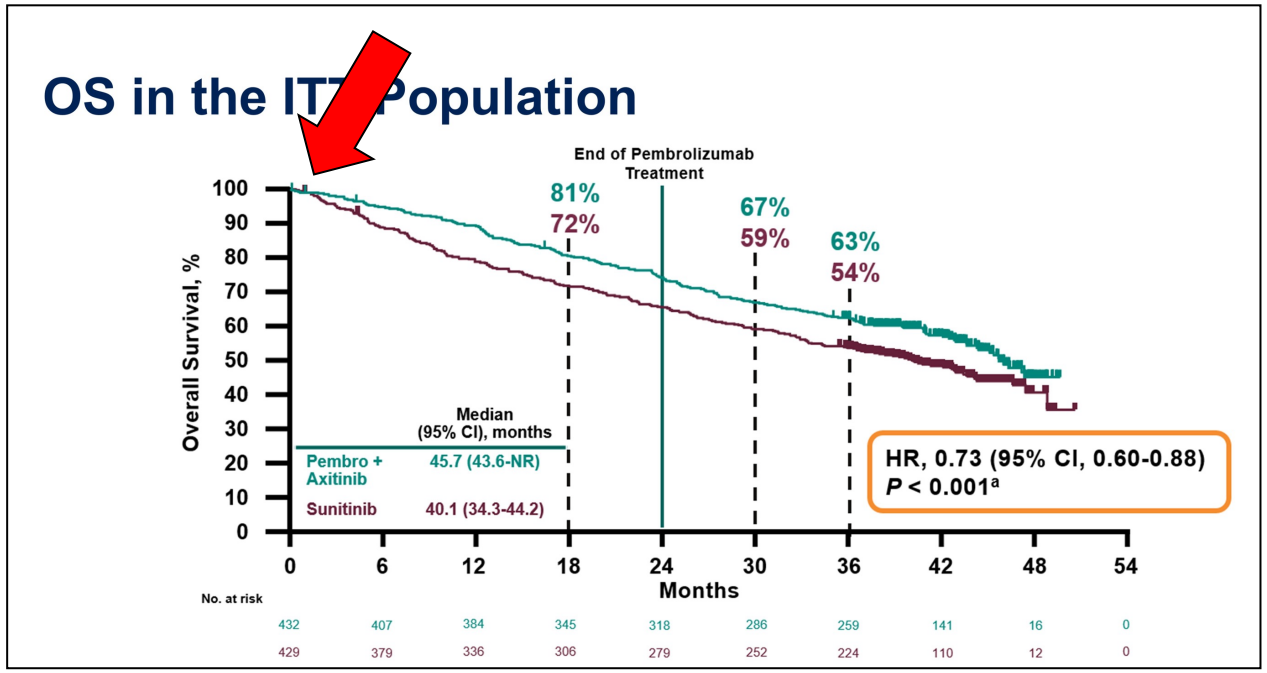
DOR, duration of response; TTR, Time to response; Ipi, Ipilimumab; Nivo, Nivolumab; Pembro, Pembrolizumab; Axi, Axitinib; Cabo, Cabozantinib; ORR, objective response rate; mPFS, median progression-free survival; HR, hazard ratio; NR, not reached; mOS, median overall survival. # Extended 5-year follow-up data, * Extended 4-year follow-up date, ## Extended 3.5-year follow-up date.

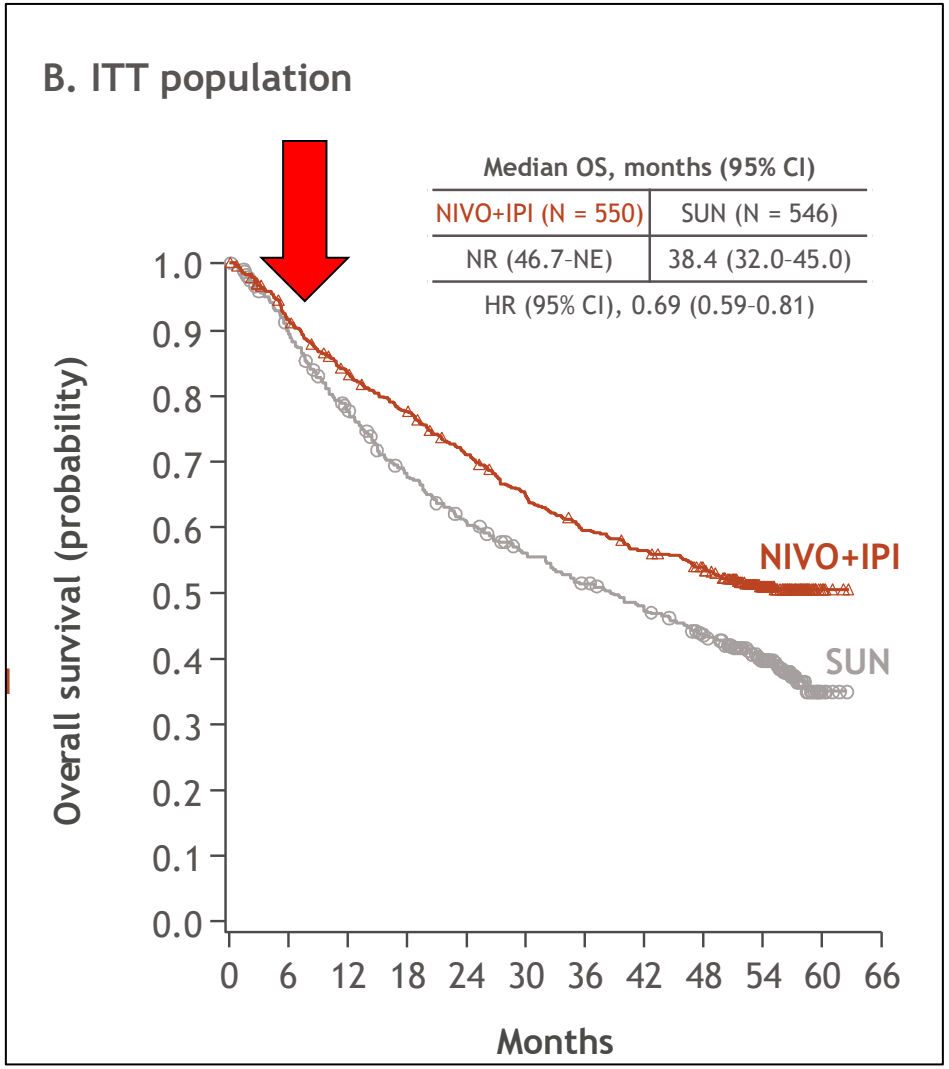
IO-IO = 39%

IO-TKI = 55-71%

Zarrabi et al., Cancers 2022

SEPARATING SURVIVAL CURVE





IO-IO = +/- 6 months

IO-TKI = < 3 months

3

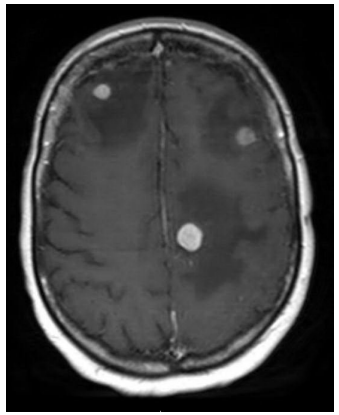
Contra-indication to corticosteroids
(allergy; not-well controlled diabetes)

PATIENTS RECEIVED HIGH- DOSE CORTICOSTEROIDS TO MANAGE ANY-GRADE irAEs

IPI + NIVO	35 %
IO + TKI	
AXI + PEMBRO	14%
CABO + NIVO	19%
LENVA + PEMBRO	15%

4

Brain metastases (especially with CABOZANTINIB)



EPIDEMIOLOGY / INCIDENCE RCC

- Majority of clinical trials limit (or strictly exclude) patients with BM
- Most data = restrospective- observational designs

STUDY	SOURCE	NO. OF PATIENTS AT RISK	YEARS	HISTOLOGY	TIME OF EVALUATION	INCIDENCE OF BM, %
Schouten 2002[15]	MCR	114	1986-1995	NR	NR	
Bianchi 2012[16]	NIS	11,157	1998-2007	NR	NR	
Wyler 2014[17]	Institutional	246	1967-1995	ccRCC	Autopsy	
Chandrasekar 2017[18]	SEER	6610	2010-2013	Mixed (42% ccRCC, 48% unknown)	Diagnosis of metastatic disease	9.80
Cagney 2017[19]	SEER	7463	2010-2013	NR	Diagnosis of metastatic disease	10.80
De Giorgi 2019[20]	EAP	389	2015-2016	Mixed (92% ccRCC)		
Flippot 2019[10]	Phase 2 trial	729	2016-2017	ccRCC		
Suarez-Sarmiento 2019[21]	Institutional	473	2011-2014	Mixed (81% ccRCC)		
Sun 2019[22]	SEER	NR	2010-2013	Mixed (78% ccRCC)	Diagnosis of metastatic disease	12.00
Bowman 2019[23]	Institutional	268	2006-2015	Mixed (94% ccRCC)	Prior to or during 1L therapy	28.4
Dudani 2021[2]	IMDC	9252	2002-2019	ccRCC	Start of 1L therapy	8.0
					Start of 1L therapy	3.0
					Start	

BM AT DIAGNOSIS

1.5%

BM AT DIAGNOSIS OF M+

15-30%

- Use of routine baseline

brain imaging highly variable

Hasanov et al., 2022

SUNITINIB **PAZOPANIB** **AXITINIB**

STUDY	TYPE OF STUDY	TARGETED AGENTS	NO. OF PATIENTS	MEDIAN OS, MO	LOCAL RESPONSE	TOXICITY
Without concomitant local therapy						
Chevreau 2014[96]	Phase 2	Sunitinib	16	6.3	ORR: 0%	19% G3-G4 AEs; no neurologic AEs
With or without concomitant local thera						
Peverelli 2019[97]						% G3-G4 AEs; no major neurologic side effects
Hirsch 2						% G3-G4 AEs; no neurologic AEs
With local therapy						
Cochran 2012[99]	Retrospective	TKI, mTORi, bevacizumab	24[a]	16.6	Local control rate at 12 mo, 93%	12.5% radiation-induced edema or necrosis
Verma 2013[92]	Retrospective	Sorafenib, sunitinib	40[a]	6.7	Local control rate at 12 mo, 69%	5% radiation necrosis
Seastone 2014[100]						
Bates 2017[101]		temsirolimus				
Johnson 2015[102]	Retrospective	TKI, mTORi, bevacizumab	24[a]	21	NA	NA
Juloori 2019[76]	Retrospective	TKI, mTORi, cytokine	376[b]	9.7	Incidence of local failure, 15%	12-mo cumulative incidence of radiation necrosis: 8%
Klausner 2019[103]	Retrospective	TKI, mTORi, immunotherapy, chemotherapy	120[b]	13.5	Local control rate at 12 mo, 92%	14% G3-G4 AEs; 7% radiation necrosis

Abbreviations: AEs, adverse events; G3-G4, grade 3 or 4; mTOR, mammalian target of rapamycin; mTORi, mTOR inhibitor; NA, not applicable; ORR, objective
[a]This cohort was treated with targeted agents.
[b]These included all patients treated with or without targeted therapy.

Penetration through BBB limited

No efficacy demonstrated

Bleeding or Thrombotic complications !!!

Hasanov et al., 2022

CABOZANTINIB

STUDY	TYPE OF STUDY	TARGETED AGENTS	NO. OF PATIENTS	MEDIAN OS, MO	LOCAL RESPONSE	TOXICITY
Without concomitant local therapy						
Chevreau 2014[96]	Phase 2	Sunitinib	16	6.3	ORR: 0%	19% G3-G4 AEs; no neurologic AEs
With or without concomitant local therapy						
Peverelli 2019[97]	Retrospective	Cabozantinib	12	8.8	ORR: 50%	36% G3-G4 AEs; no major neurologic side effects
Hirsch 2021[98]	Retrospective	Cabozantinib	Cohort 1: 33	15	ORR: 55%	17% G3-G4 AEs; no neurologic AEs
			Cohort 2: 55	16	ORR: 47%	
With local therapy						
Cochran 2012[99]			24[a]	16.6		ecrosis
Verma 2013[92]			40[a]	6.7		
Seastone 2014[100]			166[b]	NA		
Bates 2017[101]	Retrospective	Sorafenib, sunitinib, pazopanib, temsirolimus	25[a]	6.7	Local control rate, 76%	NA
Johnson 2015[102]	Retrospective	TKI, mTORi, bevacizumab	24[a]	21	NA	NA
Juloori 2019[76]	Retrospective	TKI, mTORi, cytokine	376[b]	9.7	Incidence of local failure, 15%	12-mo cumulative incidence of radiation necrosis: 8%
Klausner 2019[103]	Retrospective	TKI, mTORi, immunotherapy, chemotherapy	120[b]	13.5	Local control rate at 12 mo, 92%	14% G3-G4 AEs; 7% radiation necrosis

12pts
ORR = 50%

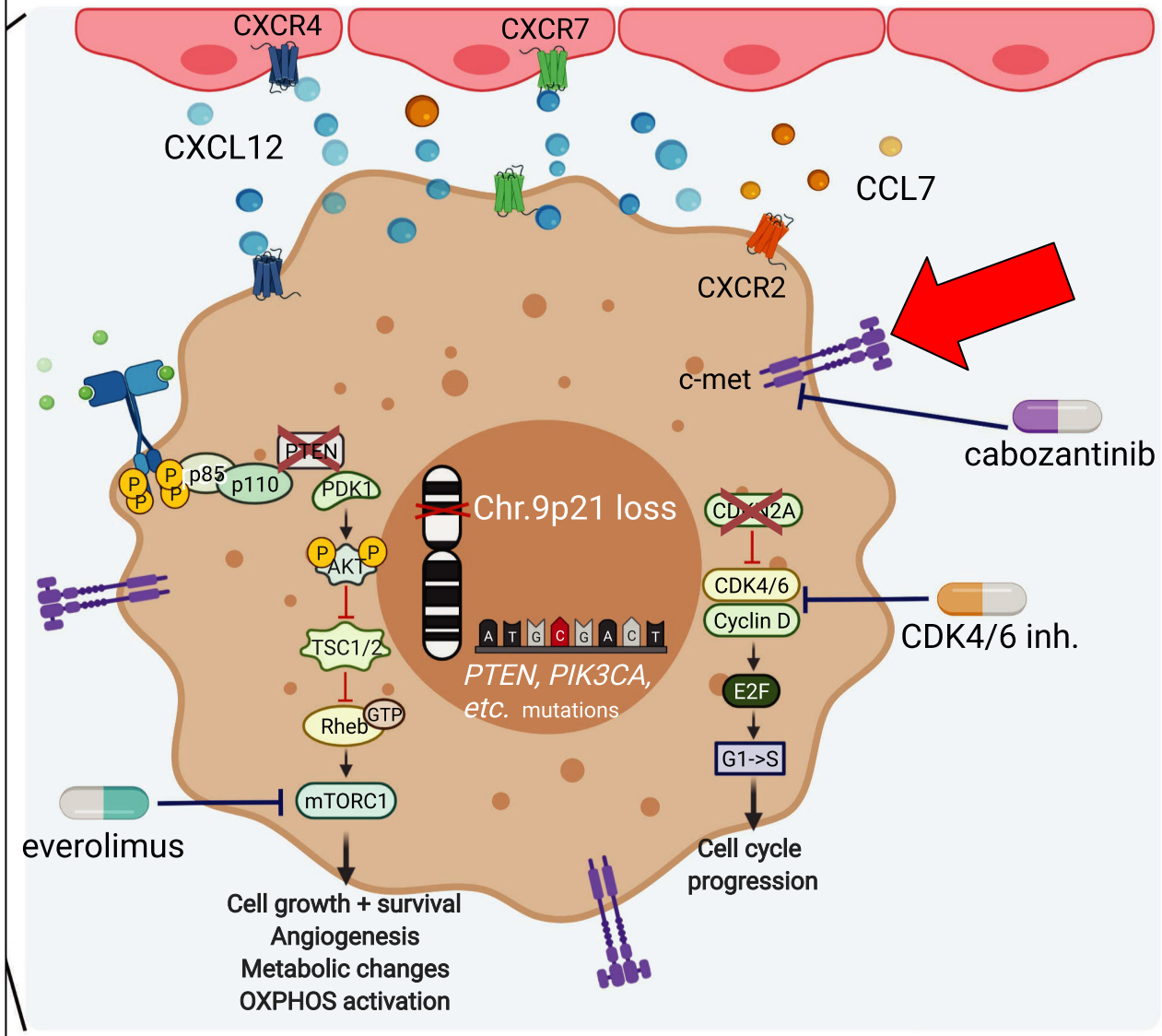
33 / 55pts
ORR = 55 / 47%

Abbreviations: AEs, adverse events; G3-G4, grade 3 or 4; mTOR, mammalian target of rapamycin; mTORi, mTOR inhibitor; NA, not applicable; ORR, objecti

[a]This cohort was treated with targeted agents.
[b]These included all patients treated with or without targeted therapy.

Hasanov et al., 2022

HETEROGENEITY BETWEEN THE SITES OF DISEASE

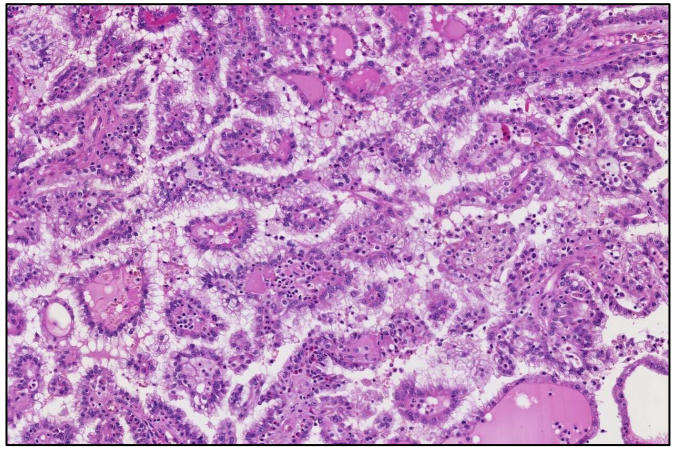


- **c-MET overexpressed in BMs compared with primary tumors or pancreatic metastases**

Hasanov et al., 2022

5

Papillary histology



CABOZANTINIB + NIVOLUMAB

PHASE II

47 pts

original reports

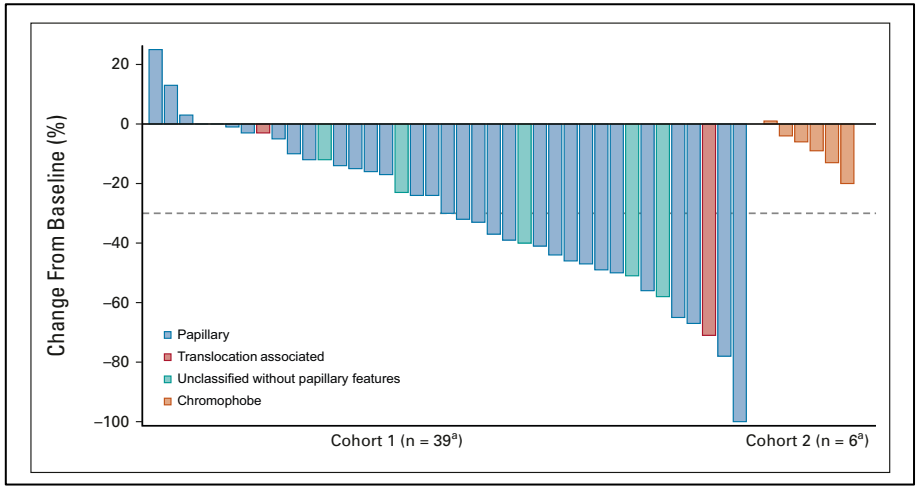
Phase II Trial of Cabozantinib Plus Nivolumab in Patients With Non–Clear-Cell Renal Cell Carcinoma and Genomic Correlates

Chung-Han Lee, MD, PhD[1,2]; Martin H. Voss, MD[1,2]; Maria Isabel Carlo, MD[1,2]; Ying-Bei Chen, MD[3]; Mark Zucker, PhD[4]; Andrea Knezevic, MS[4]; Robert A. Lefkowitz, MD[5]; Natalie Shapnik, BS[1]; Chloe Dadoun, MD[1]; Ed Reznik, PhD[4]; Neil J. Shah, MD[1,2]; Colette Ngozi Owens, MD[1]; Deaglan Joseph McHugh, MD[1,2]; David Henry Aggen, MD, PhD[1,2]; Andrew Leonard Laccetti, MD[1,2]; Ritesh Kotecha, MD[1,2]; Darren R. Feldman, MD[1,2]; and Robert J. Motzer, MD[1,2]

J Clin Oncol 40:2333-2341. © 2022

- 0-1 prior therapies
- Cohort 1 (40pts)= papillary (32pts), unclassified or translocation
- Cohort 2 (7pts) = chromophobe
- 1st endpoint = ORR

- Cohort 1 = ORR 47.5%; mOS = 28 mths
- Cohort 2 = ORR 0%; 1pt with SD >1 year



KEYNOTE B61 TRIAL

PHASE II

LENVATINIB + PEMBROLIZUMAB

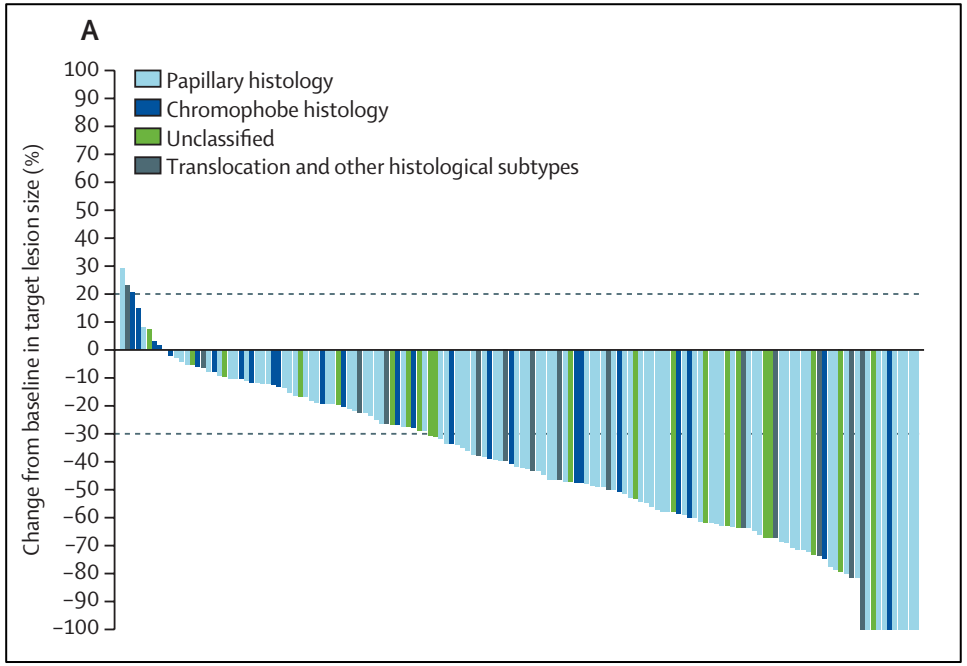
215 pts

Pembrolizumab plus lenvatinib as first-line therapy for advanced non-clear-cell renal cell carcinoma (KEYNOTE-B61): a single-arm, multicentre, phase 2 trial

Lancet Oncol 2023; 24: 881–91

Laurence Albiges, Howard Gurney, Vagif Atduev, Cristina Suarez, Miguel A Climent, David Pook, Piotr Tomczak, Philippe Barthelemy, Jae Lyun Lee, Viktor Stus, Thomas Ferguson, Pawel Wiechno, Erhan Gokmen, Louis Lacombe, Craig Gedye, Rodolfo F Perini, Manish Sharma, Xiang Peng, Chung-Han Lee**

- Untreated
- Papillary (59%); chromophobe (18%); unclassified (13%)…
- mFU = 14.9 mths
- 1st endpoint = ORR
- ORR = 44%



6

Patients with glandular (pancreas, adrenal, thyroid,…) metastases

ACTA ONCOLOGICA
2021, VOL. 60, NO. 11, 1499–1506
https://doi.org/10.1080/0284186X.2021.1962971

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Molecular underpinnings of glandular tropism in metastatic clear cell renal cell carcinoma: therapeutic implications

Eduard Roussel[a], Lisa Kinget[b], Annelies Verbiest[b], Bram Boeckx[c,d], Jessica Zucman-Rossi[e], Gabrielle Couchy[e], Stefano Caruso[e], Marcella Baldewijns[f], Steven Joniau[a], Hendrik Van Poppel[a], Diether Lambrechts[c,d], Maarten Albersen[a] and Benoit Beuselinck[b]

[a]Department of Urology, University Hospitals Leuven, Leuven, Belgium; [b]Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium; [c]Laboratory of Translational Genetics, Department of Human Genetics, KU Leuven, Leuven, Belgium; [d]VIB Center for Cancer Biology, VIB, Leuven, Belgium; [e]Inserm, UMR-1162, Génomique fonctionnelle des tumeurs solides, Institut Universitaire Hématologie, Paris, France; [f]Department of Pathology, University Hospitals Leuven, Leuven, Belgium

ABSTRACT

Background: Glandular metastases (GM) have been associated with improved survival in metastatic clear cell renal cell carcinoma (m-ccRCC). We aimed to molecularly characterize m-ccRCC with GM.

Material and methods: We performed a retrospective cohort study on all m-ccRCC patients with available tissue at our institution, diagnosed with metastatic disease from 2000 to 2019. We determined previously described angiogenesis- and immune-related gene expression signatures (GES) and ccrcc molecular subtypes through whole transcriptome RNA sequencing of primary tumors and metastases. We tested differences in GES and molecular subtypes across groups and studied overall (OS) and progression-free survival (PFS) using Kaplan–Meier survival analysis and Cox regression models.

Results: Primary tumors of patients who developed GM ($n = 55$) had higher IMmotion Angio ($p < 0.001$) and JAVELIN Angio ($p = 0.003$) GES as well as a higher proportion of angiogenic ccrcc2 molecular subtypes ($p = 0.008$) than primary tumors of patients with non-GM ($n = 128$). Metastatic lesions in glandular organs ($n = 32$) also had higher IMmotion Angio ($p = 0.008$) and JAVELIN Angio ($p = 0.02$) GES and were more frequently of the ccrcc2 molecular subtype ($p = 0.03$), compared to metastatic lesions in non-glandular organs in patients who did not develop any GM ($n = 231$), but not compared to metastatic lesions in non-glandular organs in patients who also developed GM ($n = 18$). Patients with GM had better OS (HR 0.49, $p < 0.001$) and PFS on first-line vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) (HR 0.64, $p = 0.045$) than patients with non-GM. PFS on first- or any-line immuno-oncology (IO) was not different. IMmotion Angio, JAVELIN Angio GES, and ccrcc2 molecular subtype were associated with better OS and PFS on first-line VEGFR-TKIs, but not PFS on first or any-line IO.

Conclusions: Patients with m-ccRCC who develop GM are molecularly characterized by heightened angiogenesis, translating into better prognosis and better outcomes on VEGFR-TKIs, but not IO. Based on these findings, VEGFR-TKIs should be included in the first-line treatment of m-ccRCC patients with GM.

ARTICLE HISTORY
Received 3 June 2021
Accepted 27 July 2021

KEYWORDS
Glandular metastasis; gene expression; angiogenesis; immunotherapy; molecular subtypes

- Retrospective
- 2000-2019
- Angiogenesis- and immune-signatures

- PRIMARY

GM =55

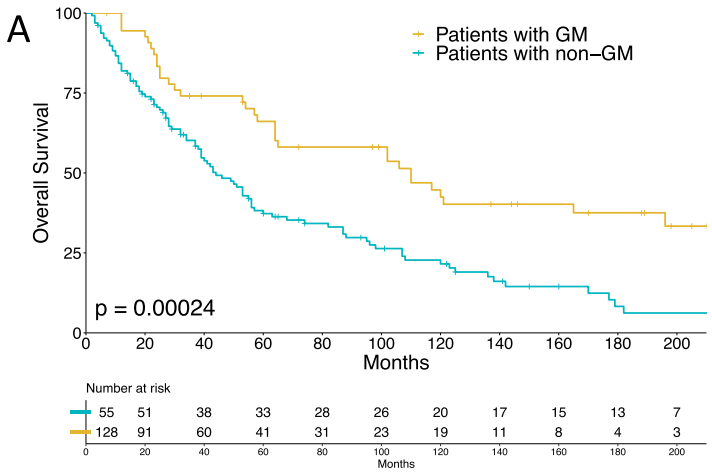
Non-GM = 128

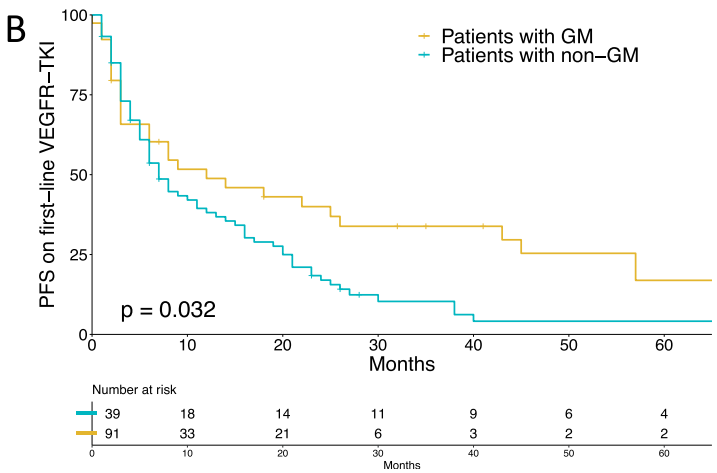
- METASTATIC

GM = 32

Non-GM = 231

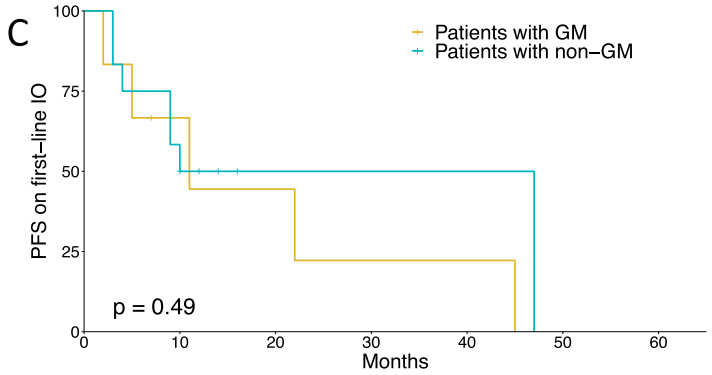
KM SURVIVAL CURVES STRATIFIED FOR PRESENCE OF GLANDULAR METASTASES

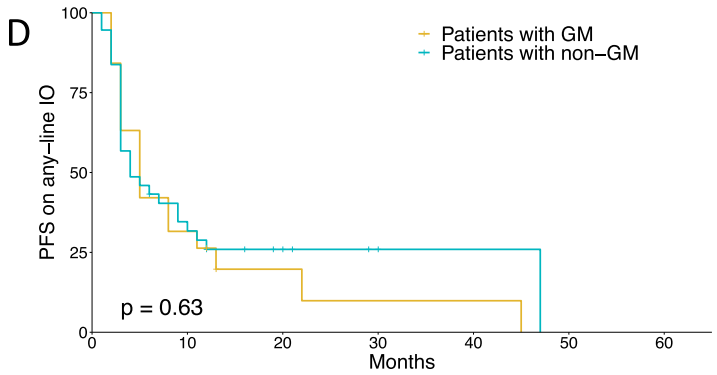




VEGFR-TKI

FIRST-LINE IO





ANY-LINE IO

- Better prognosis
- Angiogenic molecular profile
- Better outcomes on VEGR-TKIs but not IO

Metastatic renal cell carcinoma to the pancreas and other sites—a multicenter retrospective study

Cassandra Duarte,[a] Junxiao Hu,[a] Benoit Beuselinck,[b] Justine Panian,[c] Nicole Weise,[c] Nazli Dizman,[d] Katharine A. Collier,[e] Nityam Rathi,[f] Haoran Li,[f] Roy Elias,[g] Nieves Martinez-Chanza,[h] Tracy L. Rose,[i] Lauren C. Harshman,[j,p] Dharmesh Gopalakrishnan,[k] Ulka Vaishampayan,[l,q] Yousef Zakharia,[m] Vivek Narayan,[n] Benedito A. Carneiro,[o] Anthony Mega,[o] Nirmish Singla,[g,r] Cheryl Meguid,[a] Saby George,[k] James Brugarolas,[g] Neeraj Agarwal,[f] Amir Mortazavi,[e] Sumanta Pal,[d] Rana R. McKay,[c] and Elaine T. Lam[a,*]

eClinicalMedicine
2023;60: 102018

- Cohort 1 (91pts) = oligoM+ to pancreas
- Cohort 2 (229pts) = multipleM+ including pancreas

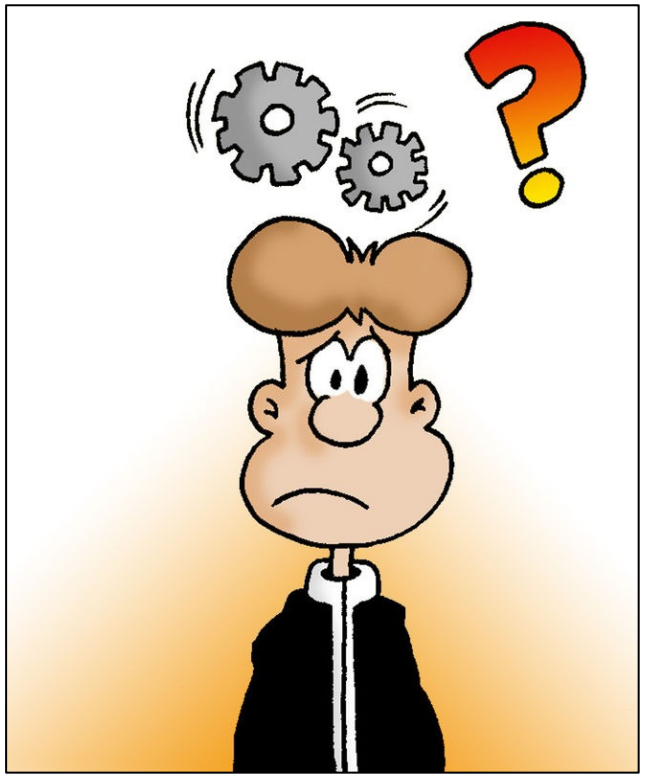
Population	Median OS (months) 95% CI
Total Cohort 1 population	121 (93, NR)
Surgery	100 (93, NR)
Systemic therapy	NR (56, NR)
Total Cohort 2 population	90.77 (74.9, 114)
Cohort A—VEGFR	90.77 (66, 114)
Cohort B—IO	92 (78, NR)
HD-IL2 Therapy	89 (78, NR)
ICI Therapy	NR (NR, NR)
Cohort C—VEGFR/IO	74.9 (33, NR)

Outcome		VEGFR subgroup	Immunotherapy subgroup	Combination VEGFR/IO subgroup
Best radiographic response Frequency (N (%))	CR	2 (1.6)	5 (13.9)	0 (0.0)
	PR	58 (45.0)	8 (22.2)	8 (50.0)
	SD	60 (46.5)	15 (41.7)	8 (50.0)
	PD	9 (7.0)	8 (22.2)	0 (0.0)
Median time on treatment (months, IQR)		11.6 (4.0, 28.1)	6.5 (3.0, 10.0)	15.0 (5.7, 21.3)

- Heightened angiogenesis
- Better outcomes (higher mOS)
- Higher PR with VEGR

+/- 50mths in all comers

WHAT IS THE BEST CANDIDATE FOR BONE METASTASES ???



BONE METASTASES INCIDENCE IN RCC FIRST-LINE STUDIES

Trial	% of patients with BM	HR (95%CI) *vs.* sunitinib (PFS)	HR (95%CI) *vs.* sunitinib (OS)
Checkmate-214[9]	20.0%	NR	0.71 (0.47-1.08)
Javelin Renal 101[10]	NR	NR	NR
KEYNOTE-426[11]	23.8%	NR	NR
CHECKMATE-9ER[12]	24.1%	0.34 (0.22-0.55)	0.54 (0.32-0.92)
CLEAR[13]	23.9%	NR	NR

BM: Bone metastases; HR: hazard ratio; NR: not reported; OS: overall survival; PFS: progression-free survival.

20-24%

BONE METASTASES OUTCOMES

Mansinho et al., 2021

CABOZANTINIB

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 12), pp: 20113-20121

Research Paper

Cabozantinib targets bone microenvironment modulating human osteoclast and osteoblast functions

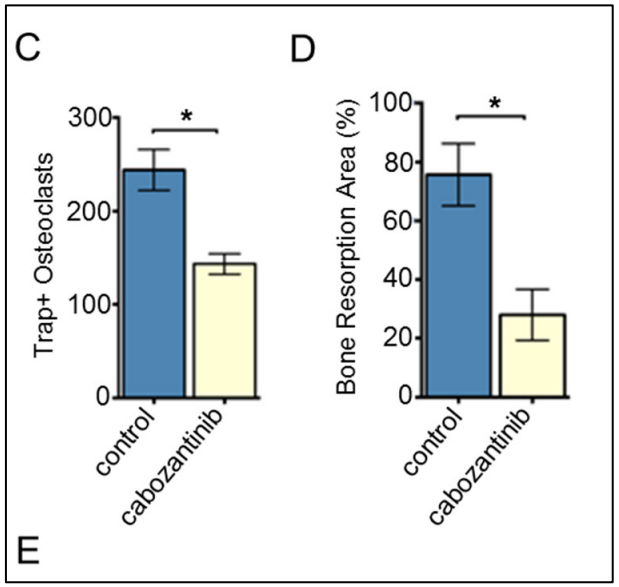
Marco Fioramonti[1,*], Daniele Santini[1,*], Michele Iuliani[1], Giulia Ribelli[1], Paolo Manca[1], Nicola Papapietro[2], Filippo Spiezia[2], Bruno Vincenzi[1], Vincenzo Denaro[2], Antonio Russo[3], Giuseppe Tonini[1], Francesco Pantano[1]

[1]Department of Medical Oncology, Campus Bio-Medico University of Rome, Rome, Italy

[2]Department of Orthopaedics and Trauma Surgery, University Campus Bio-Medico of Rome, Rome, Italy

[3]Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy

[*]These authors share first authorship and are listed in alphabetical order



- Inhibits osteoclast differentiation and bone resorption activity
- Down-modulates expression of osteoclast marker genes, TRAP-CATHEPSIN-RANK
- Increases osteoprotegerin
- Inhibits osteoclast functions « directly » and « indirectly » reducing RANKL/osteoprotegerin ratio in osteoblasts
- Increased osteoblast

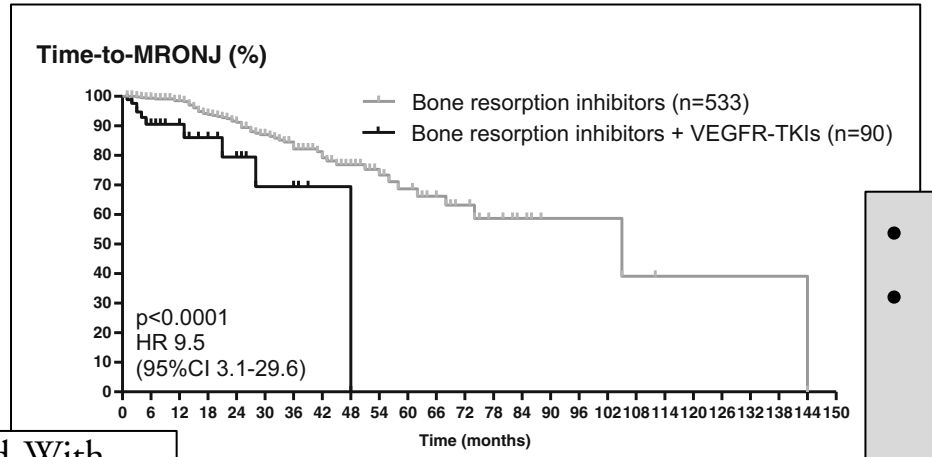
OSTEONECROSIS OF THE JAW (ONJ)

Support Care Cancer (2018) 26:869–878
DOI 10.1007/s00520-017-3903-5

ORIGINAL ARTICLE

Incidence of medication-related osteonecrosis of the jaw in patients treated with both bone resorption inhibitors and vascular endothelial growth factor receptor tyrosine kinase inhibitors

T. van Cann[1] · T. Loyson[1] · A. Verbiest[1] · P. M. Clement[1] · O. Bechter[1] · L. Willems[2] · I. Spriet[2] · R. Coropciuc[3] · C. Politis[3] · R. O. Vandeweyer[1] · J. Schoenaers[3] · P. R. Debruyne[4] · H. Dumez[1] · P. Berteloot[5] · P. Neven[5] · K. Nackaerts[6] · F. J. S. H. Woei-A-Jin[1,7] · K. Punie[1] · H. Wildiers[1] · B. Beuselinck[1]



90 pts

- Incidence = 11.1%
- During the 1st year of BRI-exposure, 1.1 % vs 6.7% (p=0.0035; OR= 5.9)
- Time to-ONJ incidence shorter in pts with AA+BRI (4.5 vs 25mths)

Denosumab Toxicity When Combined With Anti-angiogenic Therapies on Patients With Metastatic Renal Cell Carcinoma: A GETUG Study

Aline Guillot,[1] Charlotte Joly,[2] Philippe Barthélémy,[3] Emeline Meriaux,[4] Sylvie Negrier,[5] Damien Pouessel,[6] Christine Chevreau,[7] Hakim Mahammedi,[8] Nadine Houede,[9] Guilhem Roubaud,[10] Gwenaelle Gravis,[11] Sophie Tartas,[12] Laurence Albiges,[13] Cécile Vassal,[1] Mathieu Oriol,[1] Fabien Tinquaut,[14] Sophie Espenel,[15] Wafa Bouleftour,[1] Stéphane Culine,[6] Karim Fizazi[13]

Abstract

The aim of this multicenter retrospective study is to analyze the toxicity profile (mainly osteonecrosis of the jaw) of patients with metastatic renal cell carcinoma treated with denosumab and anti-angiogenic combination. Of 41 patients enrolled in this study, 7 patients developed osteonecrosis of the jaw. This toxicity signal should warn physicians about this combination in the population with metastatic renal cell carcinoma.

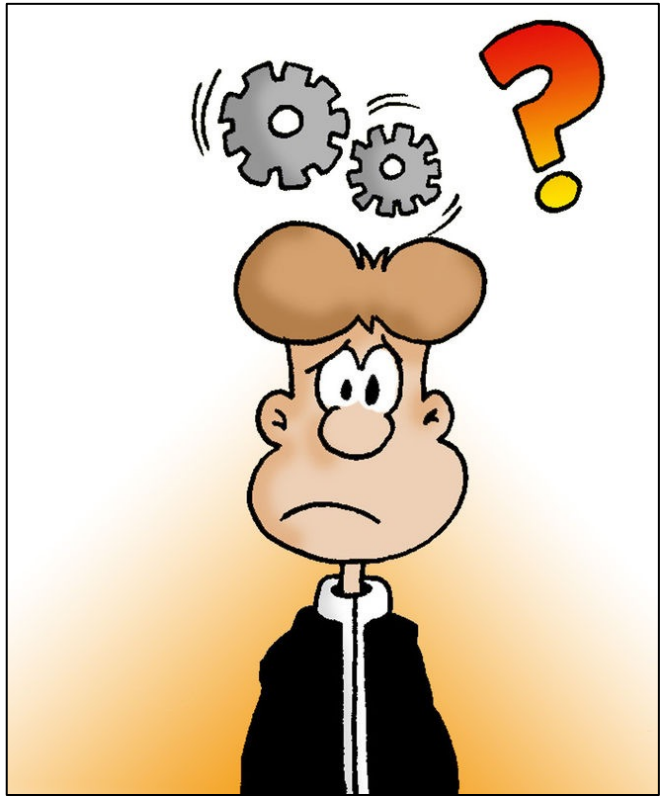
Background: About one-third of patients with renal cell carcinoma (RCC) have detectable metastases at diagnosis. Among them, bone is the second most frequent metastatic site. Treatment of metastatic RCC mostly relies on anti-angiogenic (AA) therapies and, more recently, immunotherapy. Skeletal-related events (SREs) can be prevented with bone-targeted therapies such as denosumab (Dmab), which has demonstrated superiority when compared with zoledronic acid in solid tumors. However, there is limited available data on Dmab toxicity in combination with AA therapies in patients with kidney cancer. The objective of this study was to retrospectively analyze the toxicity profile (mainly osteonecrosis of the jaw [ONJ] and hypocalcemia) in patients with metastatic renal cell carcinoma (mRCC) treated with Dmab and AA therapy combination. **Patients and Methods:** We conducted a multicenter retrospective study among centers from the French Groupe d'Etudes des Tumeurs Uro Genitales (GETUG). Patients with bone metastases who received concurrently or sequentially AA therapy and Dmab were included in this study. **Results:** A total of 41 patients with mRCC were enrolled. Although no patient presented with severe hypocalcemia, ONJ occurred in 7 (17%) of 41 patients. Interestingly, all patients with ONJ received the Dmab and AA combination in the first line of treatment; among these patients, 3 patients had no risk factor other than the Dmab and AA combination. **Conclusion:** The incidence of ONJ was high in this real-life population of patients with mRCC treated with AA therapies combined with Dmab. This toxicity signal should warn physicians about this combination in the mRCC population.

Clinical Genitourinary Cancer, Vol. 17, No. 1, e38-43
Keywords: Anti-angiogenic therapies, Bone metastasis, Desosumab, Metastatic renal cell carcinoma, Osteonecrosis of the jaw

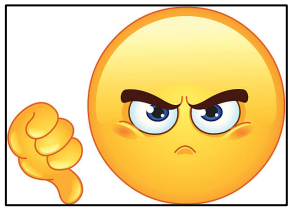
41 pts

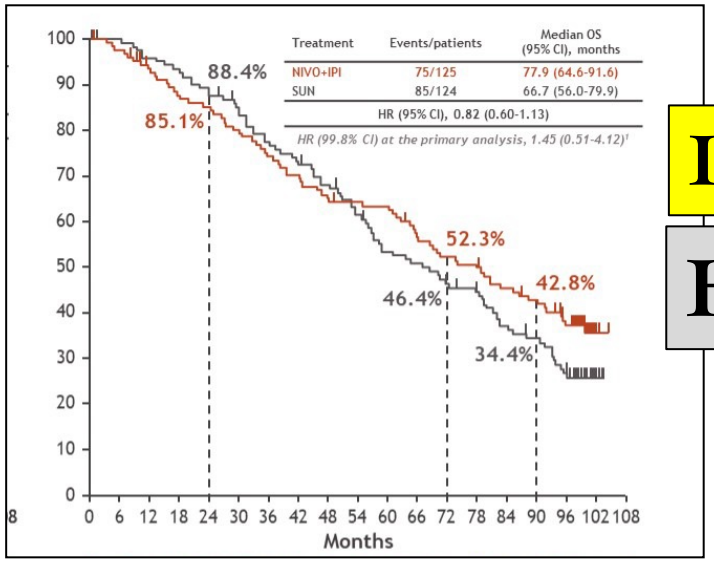
- ONJ = 17%
- All pts with ONJ received DENO + AA

WHAT IS THE BEST CANDIDATE FOR FAVORABLE IMDC RISK GROUP ???



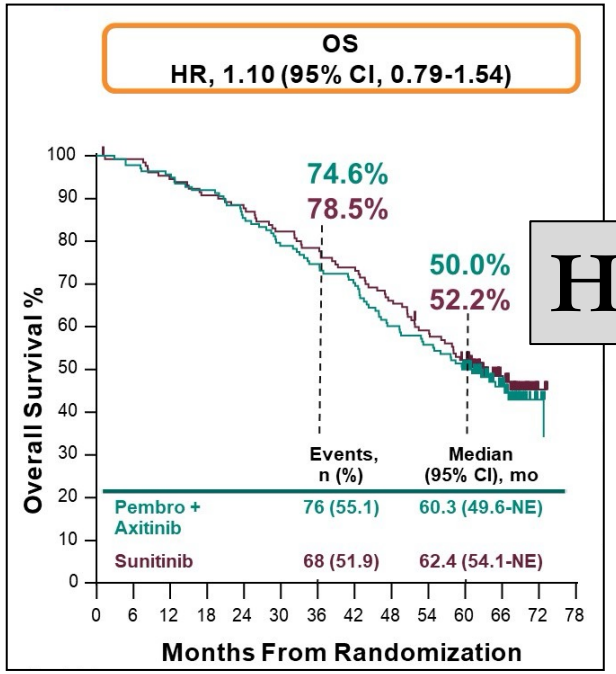
OS / PHASE III RCTs





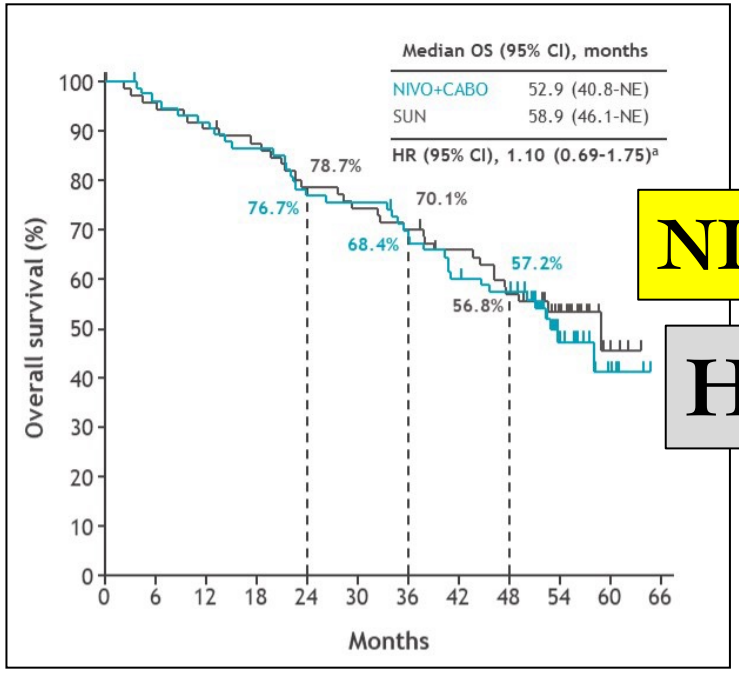
IPI +NIVO

HR = 0.82 (NS)



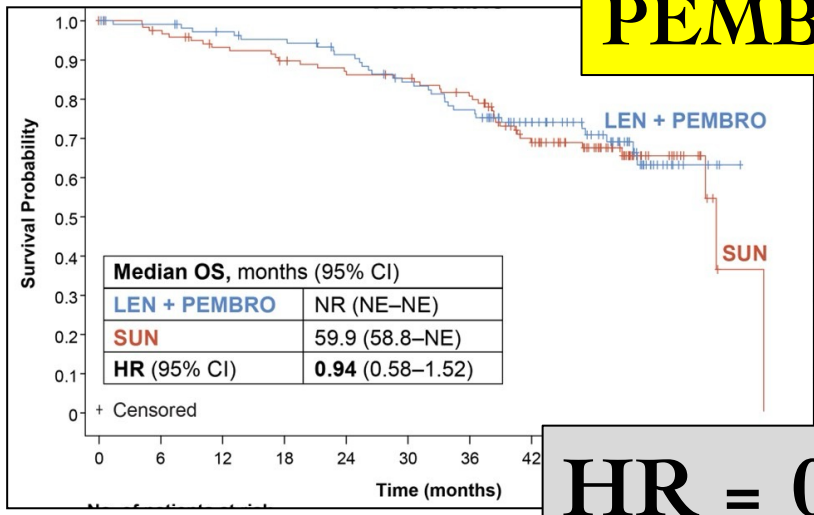
PEMB + AXI

HR = 1.10 (NS)



NIVO +CABO

HR = 1.10 (NS)



PEMB +LENVA

HR = 0.94 (NS)

REIMBURSEMENT CRITERIA

NIVO + CABO

PEMB + AXI

VERY FAVORABLE RISK GROUP

ASCO GU 2021- abstract 339

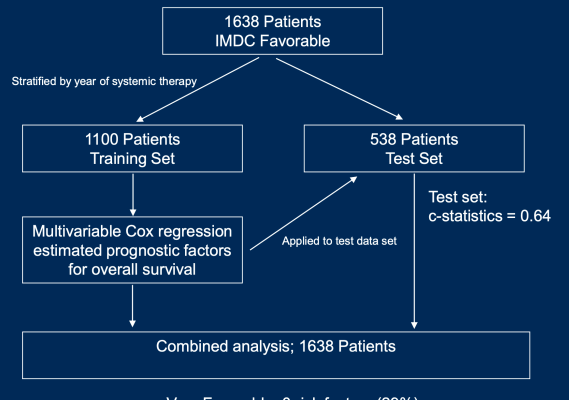
1638 pts

Study Design

Training set:
3 risk factors for OS
HR: 1.4~1.5; p-values<0.05

Risk Factor	1	0
Primary diagnosis to systemic therapy	< 3 yr	≥ 3 yr
Karnofsky Performance Status	80%	> 80%
Presence of brain, liver or bone metastasis	Yes	No

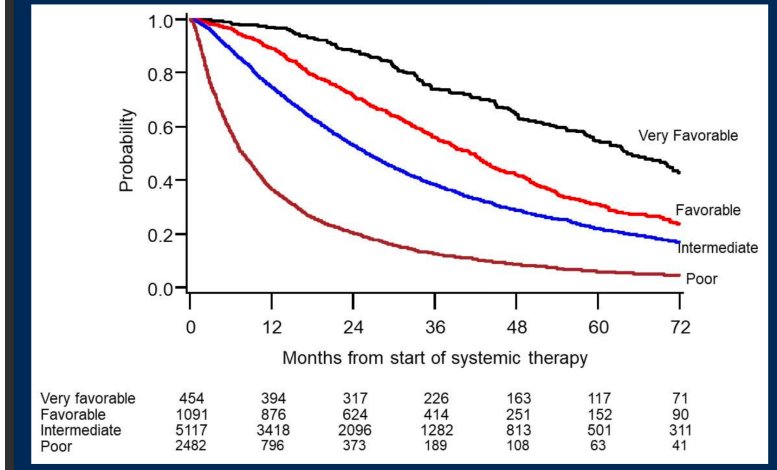
0 risk factors = very favorable risk
≥1 risk factor = favorable risk



Very Favorable: 0 risk factors (29%)
Favorable: ≥ 1 risk factors (71%)

Correlation to underlying biology !!!

Overall Survival

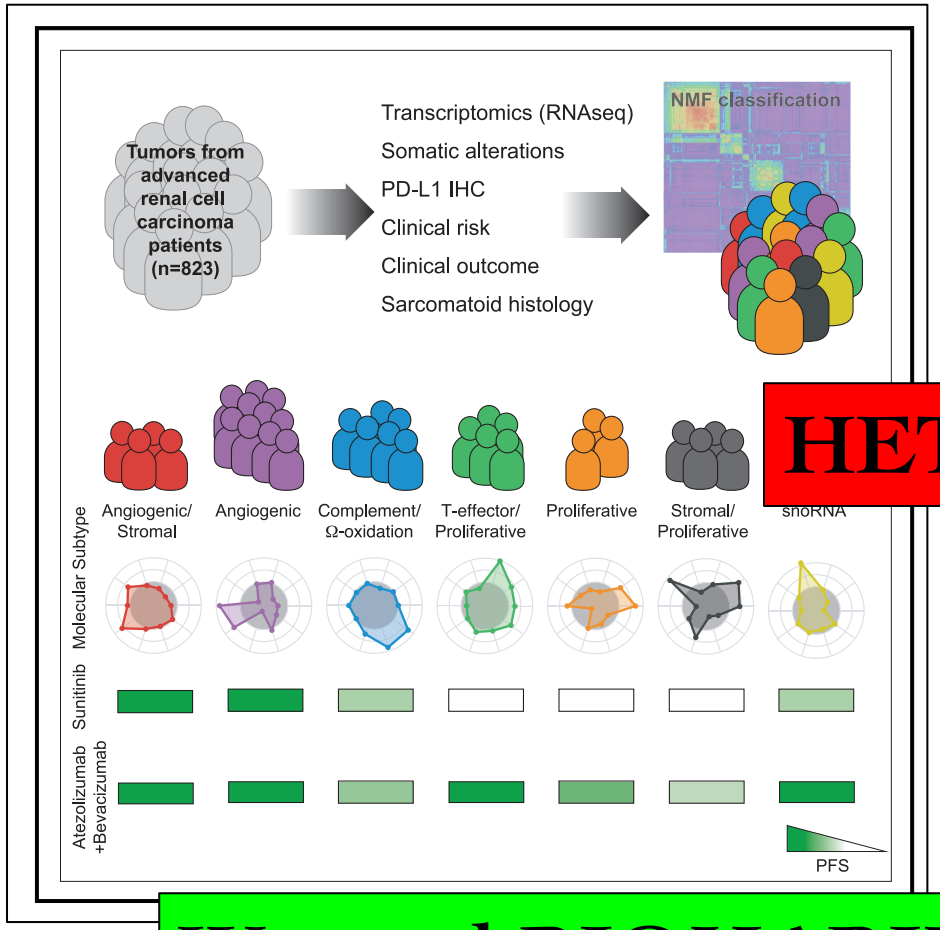


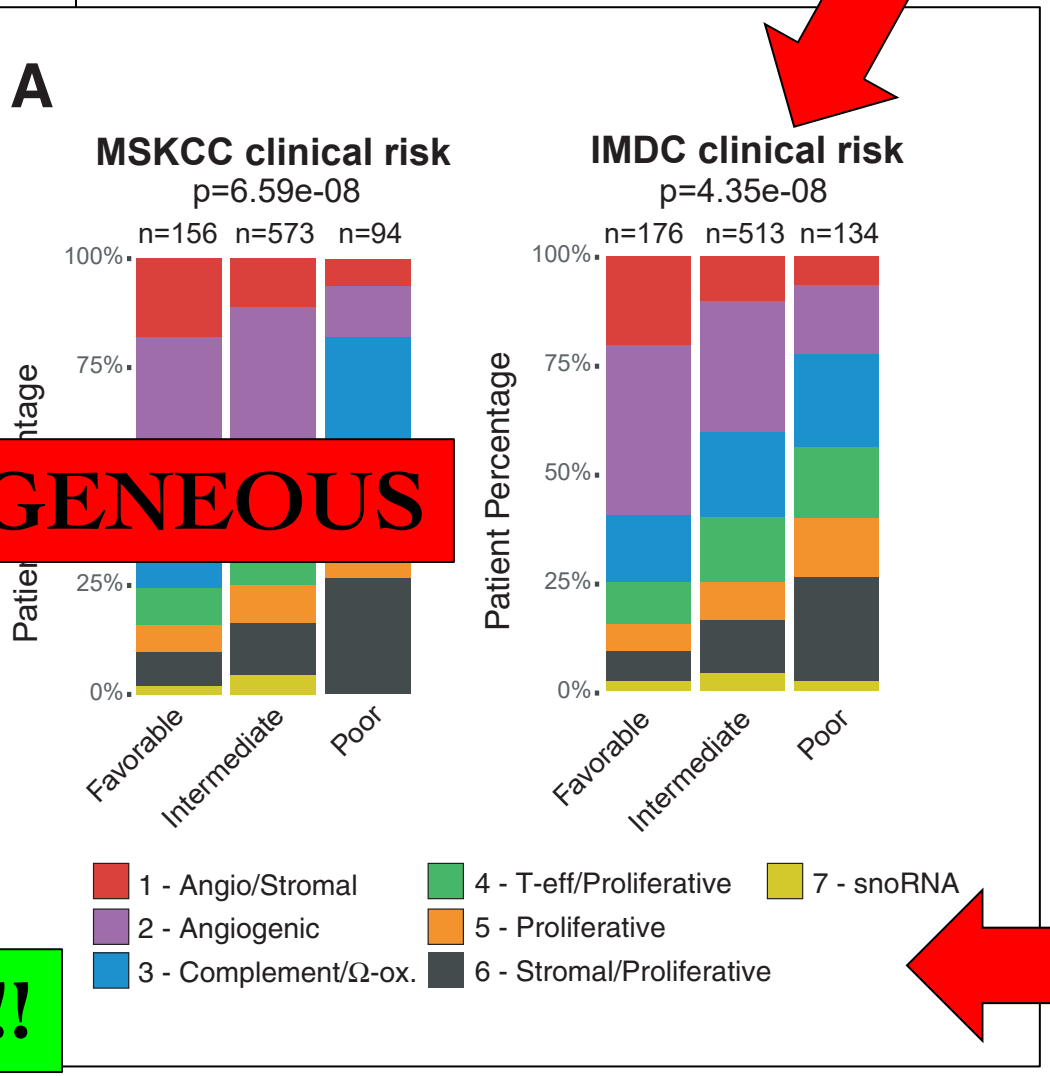
	Very Favorable (n=454)	Favorable (n=1091)	Hazard ratio (95% CI) p-value
Median OS, months (95% CI)	64.8 (58.8 - 70.8)	45.6 (42.0 - 50.4)	1.84 (1.56 - 2.20) <0.001
Median time to treatment failure, months (95% CI)	16.3 (14.8 - 18.2)	12.0 (11.2 - 12.9)	1.31 (1.16 - 1.48) <0.001

Molecular Subsets in Renal Cancer Determine Outcome to Checkpoint and Angiogenesis Blockade

Robert J. Motzer,[1,11,*] Romain Banchereau,[2,11] Habib Hamidi,[2] Thomas Powles,[3] David McDermott,[4] Michael B. Atkins,[5] Bernard Escudier,[6] Li-Fen Liu,[2] Ning Leng,[2] Alexander R. Abbas,[2] Jinzhen Fan,[2] Hartmut Koeppen,[2] Jennifer Lin,[2] Susheela Carroll,[7] Kenji Hashimoto,[8] Sanjeev Mariathasan,[2] Marjorie Green,[2] Darren Tayama,[2] Priti S. Hegde,[9] Christina Schiff,[2] Mahrukh A. Huseni,[2,12,13,*] and Brian Rini[10,12]

Cancer cell, 2020



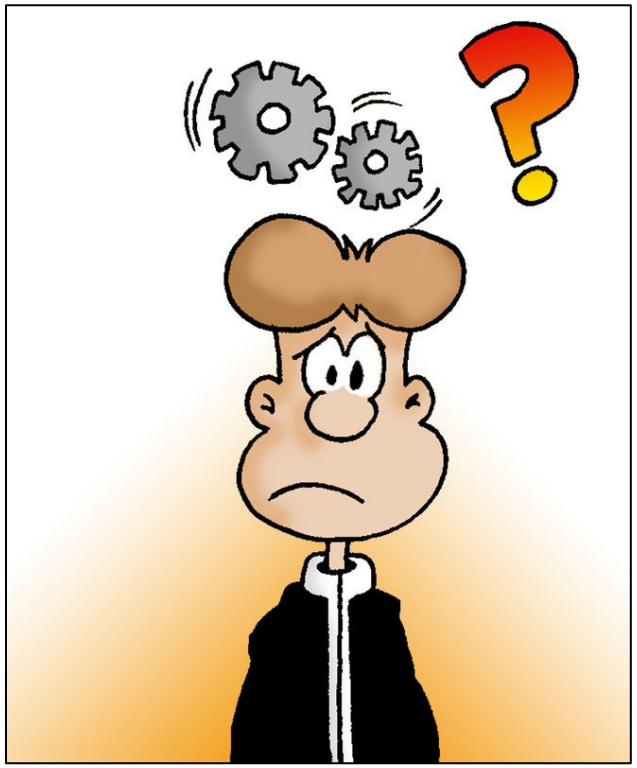


HETEROGENEOUS

We need BIOMARKERS !!!

THE OPTIMAL TREATMENT OF IMDC GOOD-FAVORABLE RISK RCC PATIENTS ?

BENEFITS OF INTENSIFICATION WITH « TRIPLET » ???



CHECKMATE 9ER- TRIPLET ARM

50 pts

mFU = 39.1 mths

European Journal of Cancer 177 (2022) 63–71

Available online at www.sciencedirect.com

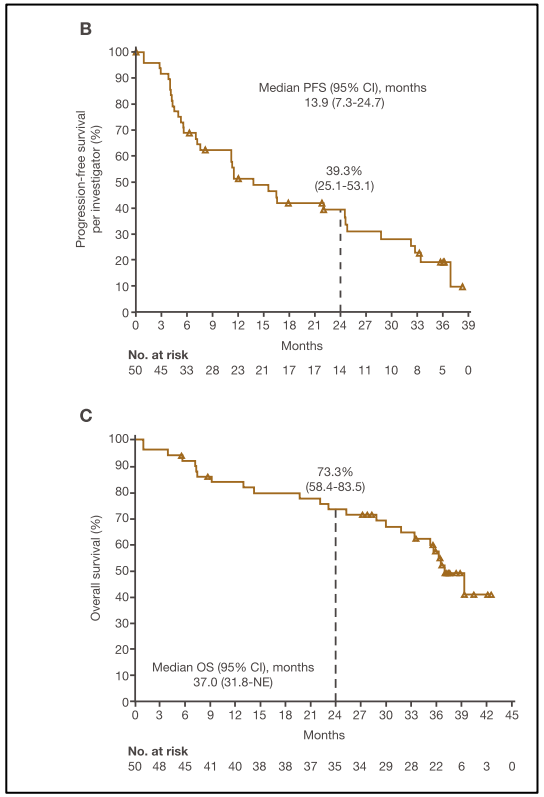
ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Nivolumab plus ipilimumab plus cabozantinib triplet combination for patients with previously untreated advanced renal cell carcinoma: Results from a discontinued arm of the phase III CheckMate 9ER trial

Andrea B. Apolo [a,*], Thomas Powles [b], Bernard Escudier [c], Mauricio Burotto [d], Joshua Zhang [e], Burcin Simsek [f], Christian Scheffold [g], Robert J. Motzer [h,1], Toni K. Choueiri [i,1]



- Exploratory analysis of pts randomised to the triplet arm (IPI+NIVO+CABO) before enrolment discontinuation

- ORR = 44%; CR = 8%
- mPFS = 13.9 mths
- mOS = 37 mths
- Grade 3-4 TRAEs = 84% !!!
- ASAT, ALAT, hepatotoxicity
- 46% of treatment discontinuation

of at least one study drug due to AEs

COSMIC-313 TRIAL

PHASE III

855 pts

mFU = 20 mths

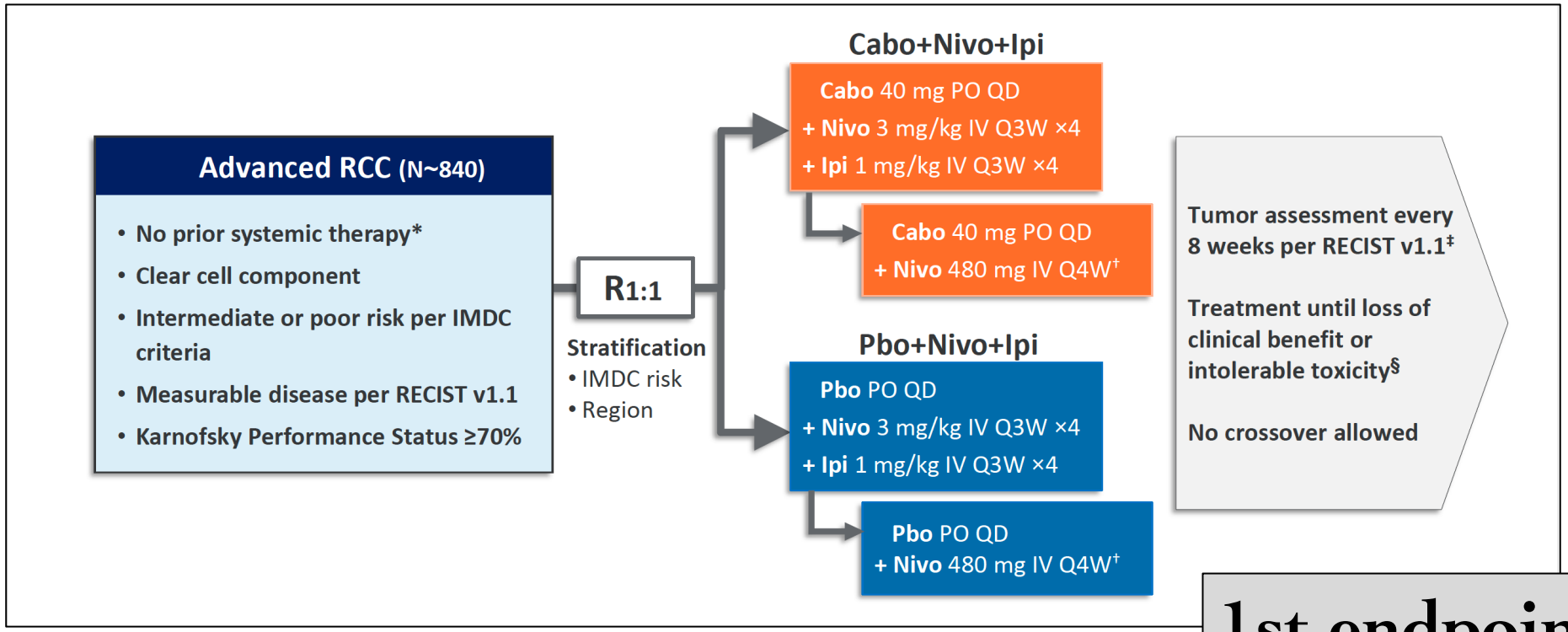
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cabozantinib plus Nivolumab and Ipilimumab in Renal-Cell Carcinoma

T.K. Choueiri, T. Powles, L. Albiges, M. Burotto, C. Szczylik, B. Zurawski, E. Yanez Ruiz, M. Maruzzo, A. Suarez Zaizar, L.E. Fein, F.A. Schutz, D.Y.C. Heng, F. Wang, F. Mataveli, Y.-L. Chang, M. van Kooten Losio, C. Suarez, and R.J. Motzer, for the COSMIC-313 Investigators*

May 2023



1st endpoint = PFS

ADVERSE EVENTS (SAFETY POPULATION)

	Cabo+Nivo+Ipi (N=426)		Pbo+Nivo+Ipi (N=424)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse events				
Any event,* %	99	73	91	41
Alanine aminotransferase increased	46	26	17	6
Aspartate aminotransferase increased	44	20	16	5
Diarrhea	41	4	18	3
Palmar-plantar erythrodysesthesia	28	3	4	0
Hypothyroidism	24	<1	15	0
Hypertension	23	8	5	2
Fatigue	22	2	21	1
Lipase increased	22	9	13	6
Amylase increased	20	5	12	2
Rash	20	2	20	1
Pruritus	20	0	26	<1

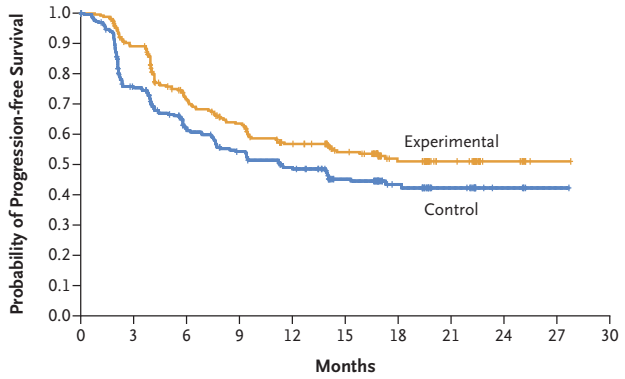
Grade 3-4 = 73% vs 41%

	Cabo+Nivo+Ipi (N=426)	Pbo+Nivo+Ipi (N=424)
Median duration of exposure of study treatment (range), mo	10.9 (0.2–28.5)	10.3 (0.1–28.1)
Median average daily dose (range) of Cabo or Pbo, mg	23.2 (3.6–40.0)	36.1 (0.8–40.0)
Median Nivo infusions (range) received, no	10 (1–27)	9 (1–27)
Doses of Ipi received, %		
4	58	73
3	13	14
2	22	7
1	7	6
Any dose hold due to an AE, %	90	70
Any dose reduction of Cabo or Pbo due to an AE, %	54	20
Treatment-related AE leading to discontinuation, %		
Any study treatment	45	24
Cabo or Pbo	28	14
Nivo	26	18
Ipi	30	12
All treatment components (due to the same AE)	12	5

TRAEs leading to discontinuation (any treatment) = 45% vs 24%

Use of High-dose corticosteroids = 58% / 35%

PFS / FINAL ANALYSIS / ALL



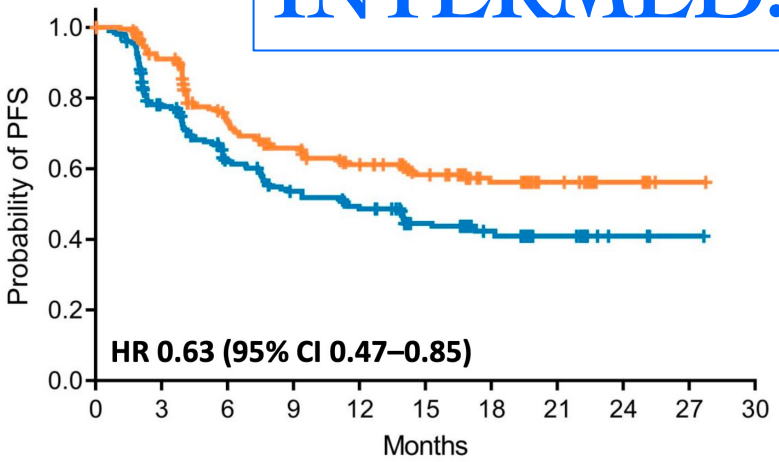
	No. of Patients	No. of Events	Median Progression-free Survival
			mo
Experimental	276	116	NR (14.0–NE)
Control	274	133	11.3 (7.7–18.2)

Hazard ratio for disease progression or death, 0.73 (95% CI, 0.57–0.94)
P=0.01

Variable	Experimental (N=276)	Control (N=274)
Objective response (95% CI) — %	43 (37–49)	36 (30–42)
Best overall response — no. (%)		
Complete respo		
Partial respons		
Stable disease		
Progressive dis		
Could not be ev		
Disease control — no. (%)†	238 (86)	198 (72)
Median time to response (range) — mo	2.4 (1.5–17.1)	2.3 (1.9–16.8)
Median duration of response (95% CI) — mo	NR (20.2–NR)	NR (NE–NE)

Excess toxicity seen in the triplet arm ➔ no adequate treatment exposure ➔ limiting the benefit ?

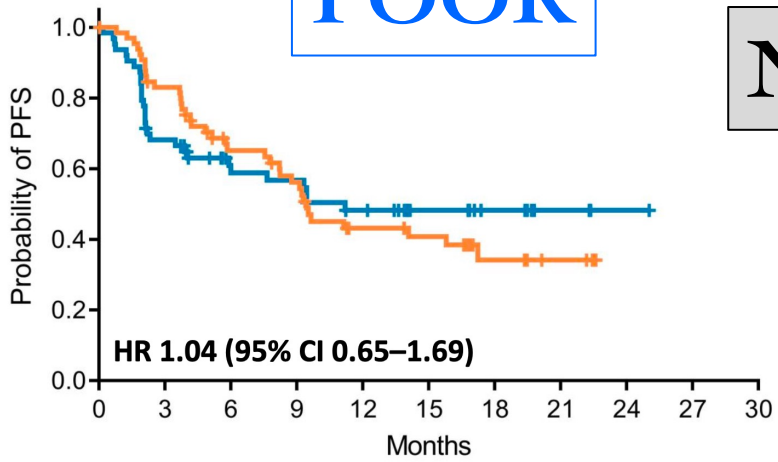
INTERMED.



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=209)	79	NR (16.9–NE)
Pbo+Nivo+Ipi (N=208)	103	11.4 (7.6–17.3)

ORR: 45% (95% CI, 38.1–52.0) for Cabo+Nivo+Ipi vs 35% (95% CI, 28.6–42.0) for Pbo+Nivo+Ipi

POOR



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=67)	37	9.5 (7.8–17.3)
Pbo+Nivo+Ipi (N=66)	30	11.2 (4.0–NE)

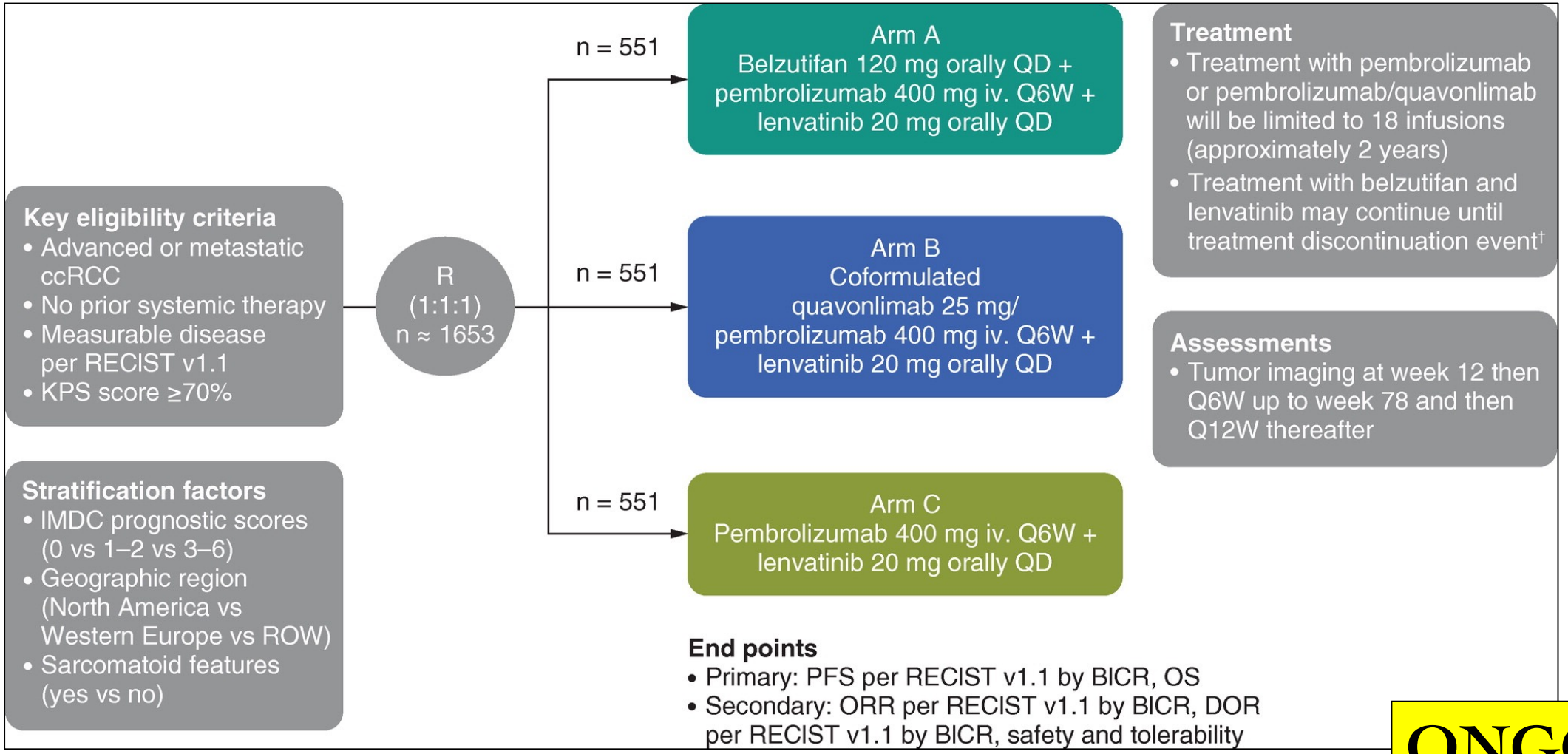
ORR: 37% (95% CI, 25.8–50.0) for Cabo+Nivo+Ipi vs 38% (95% CI, 26.2–50.7) for Pbo+Nivo+Ipi

NS

- Highest rates of IMDC poor risk patients (25%)
- More patients without nephrectomy
- No IMDC favorable risk patients (0%)

LITESPARK-012 TRIAL

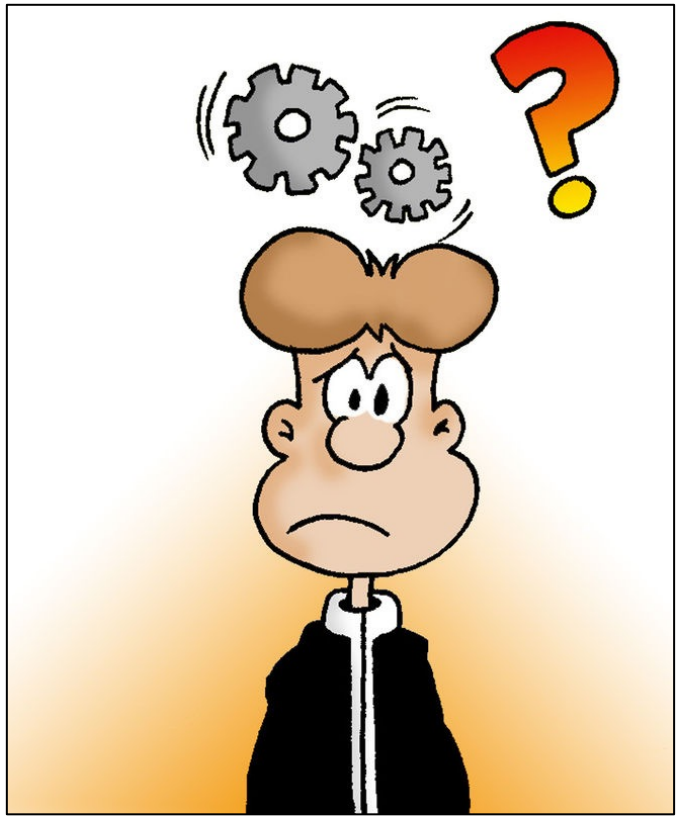
PHASE III



ONGOING

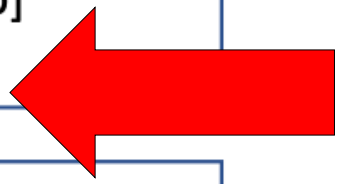
BELZUTIFAN = Manageable safety profile

STILL PLACE FOR TKI MONOTHERAPY ???



INTERNATIONAL GUIDELINES (EAU)

	Standard of Care	Alternative in patients who can not receive or tolerate immune checkpoint inhibitors
IMDC favourable risk	nivolumab/cabozantinib [1b] pembrolizumab/axitinib [1b] pembrolizumab/lenvatinib [1b]	sunitinib* [1b] pazopanib* [1b]
IMDC intermediate and poor risk	nivolumab/cabozantinib [1b] pembrolizumab/axitinib [1b] pembrolizumab/lenvatinib [1b] nivolumab/ipilimumab [1b]	cabozantinib* [2a] sunitinib*[1b] pazopanib* [1b]

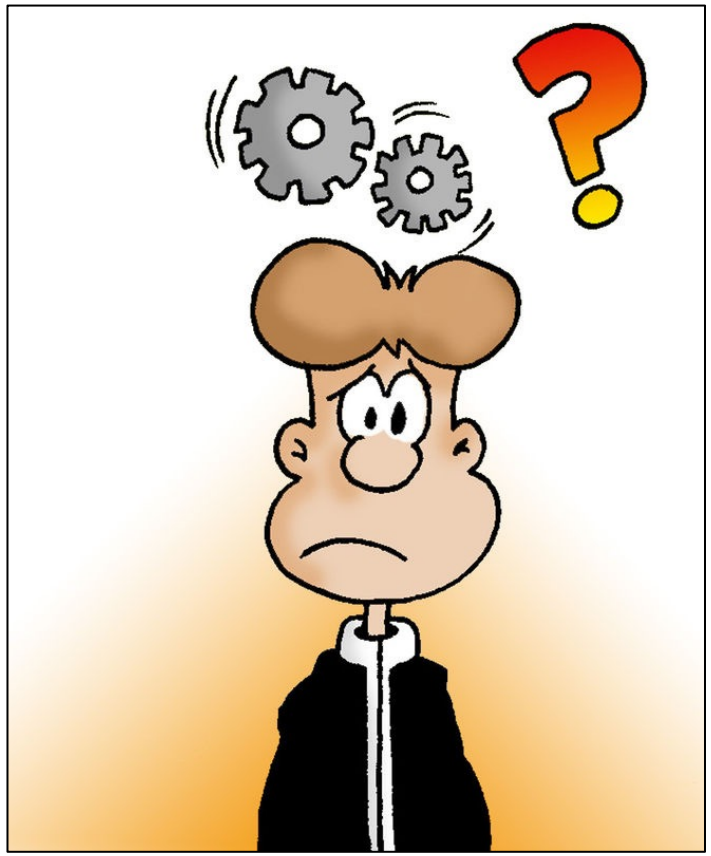


PATIENTS FOR MONOTHERAPY ?

- significant comorbidities = immunosuppressed transplant recipients; severe autoimmune diseases
- unable to tolerate the added toxicity associated with combinaison (elderly and unfit)

- Clearly defined angiogenic profile (but need of biomarkers)
- Very favorable risk group ? (but also need of biomarkers)

WHAT ABOUT TAILORED APPROACH ??



OMNIVORE TRIAL

PHASE II

83 / 42 pts (L1)

original reports

Optimized Management of Nivolumab and Ipilimumab in Advanced Renal Cell Carcinoma: A Response-Based Phase II Study (OMNIVORE)

Rana R. McKay, MD[1]; Bradley A. McGregor, MD[2]; Wanling Xie, MS[2]; David A. Braun, MD, PhD[2]; Xiao Wei, MD[2]; Christos E. Kyriakopoulos, MD[3]; Yousef Zakharia, MD[4]; Benjamin L. Maughan, MD, PharmD[5]; Tracy L. Rose, MD[6]; Walter M. Stadler, MD[7]; David F. McDermott, MD[8]; Lauren C. Harshman, MD[2]; and Toni K. Choueiri, MD[2]

JCO 2020

mFU = 19.5 mths

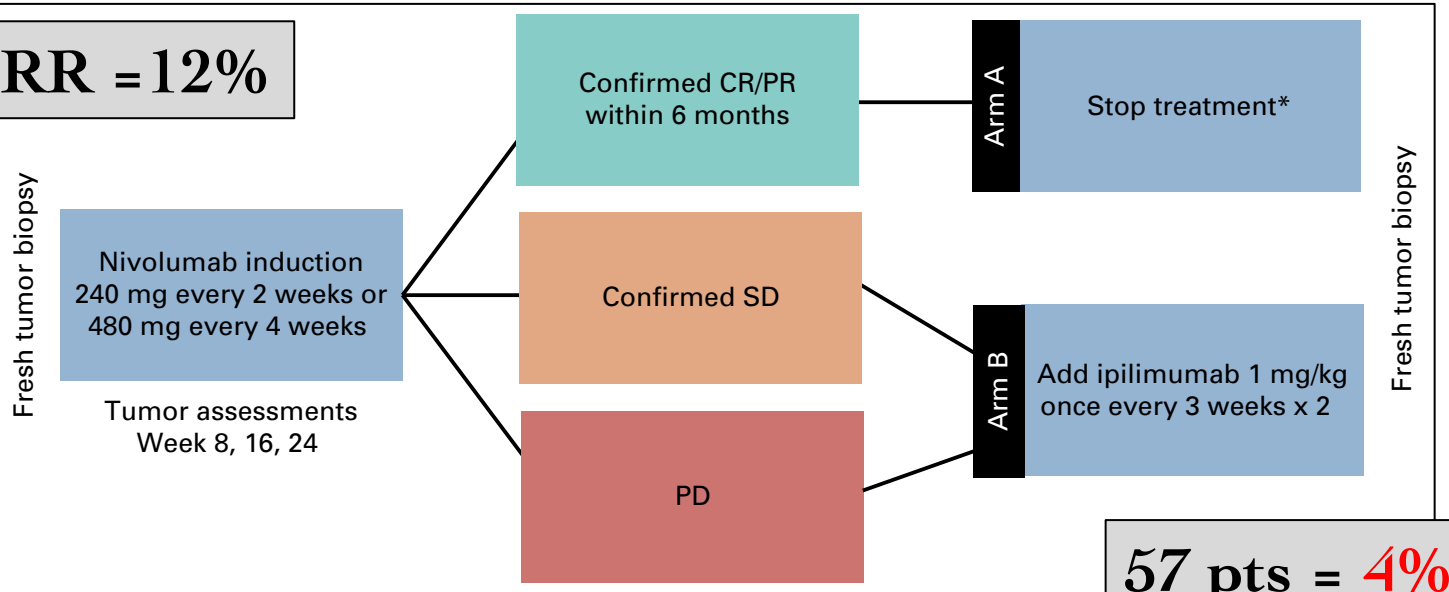
1st endpoint = ORR

12pts = 42% remained off NIVO at > 1 year

ORR =12%

Key inclusion criteria:

- Metastatic RCC
- Any RCC histology
- Untreated or previously treated
- No prior CPI
- Measurable disease by RECIST version 1.1
- ECOG PS 0-2

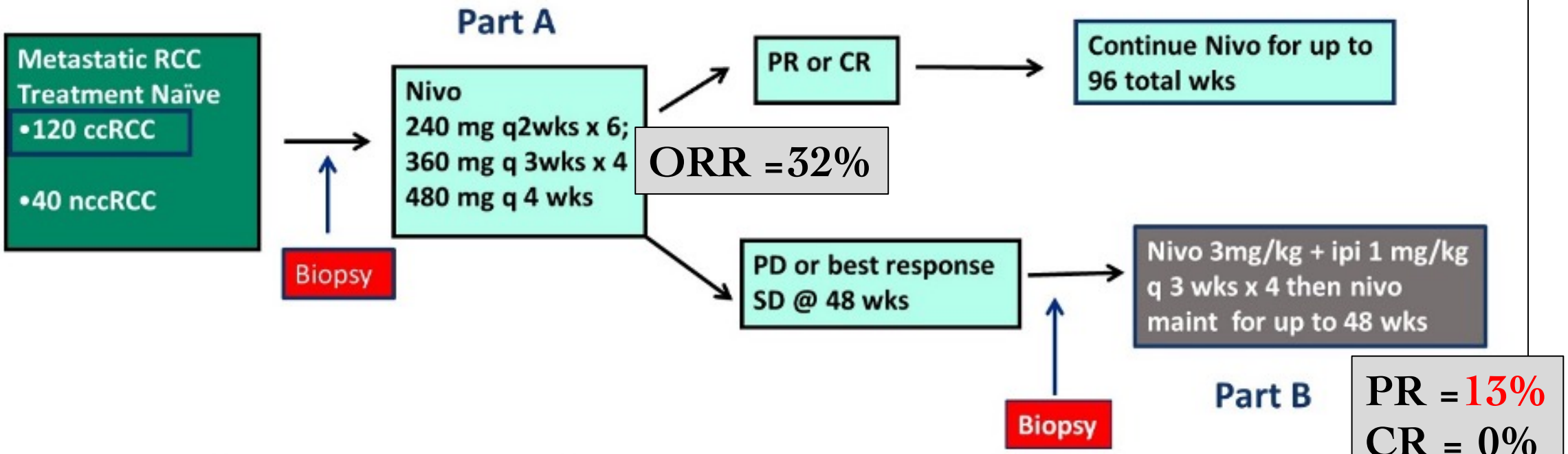


57 pts = 4% of PR; no CR

HCRN GU16-260 TRIAL | PHASE II | 123 pts L1

mFU = 26.9 mths

IIT at 12 sites conducted through the HCRN GU Group
Support provided by BMS (CM209-669)



Extensive Biomarker studies in collaboration with the DFHCC
Kidney Cancer SPORE
DOD Translational Partnership Grant (Atkins, Wu)

Scans q12 weeks; Confirm response and PD;
Measurements by RECIST 1.1
Mandatory biopsies

TITAN TRIAL | **PHASE II** | **207 / 108 pts (L1)** | **mFU = 36.2 wks**

Tailored ImmunoTherapy Approach with Nivolumab in RCC (TITAN-RCC)

n=200

Key Inclusion Criteria

- Metastatic/locally advanced RCC, histologically confirmed
- Clear cell component
- Intermediate/high risk by IMDC
- Untreated or pretreated with 1 prior TKI (⇨ 1st or 2nd line*)
- Measurable disease as per RECIST v1.1
- KPS ≥ 70
- Evaluable tumor sample for PD-L1 expression (Dako PD-L1 IHC 28-8 pharmDx antibody, central lab)

* Independent cohorts

EudraCT number: 2016-002307-26

ORR = 29%

Tumor Assessments week 8, week 16

Nivolumab Induction
N_{alone} (240 mg Q2W x 8)

Early PD (week 8)

Tumor Assessments after 6 weeks, every 12 weeks thereafter

CR/PR → **Nivolumab Maintenance**
N_{alone} (240 mg Q2W)

SD/PD → **Nivolumab+Ipilimumab "Boost" 1+2**
$N_{3mg/kg}$ + $I_{1mg/kg}$ (Q3W x 2)

CR/PR → Nivolumab Maintenance

SD/PD → **Nivolumab+Ipilimumab "Boost" 3+4**
$N_{3mg/kg}$ + $I_{1mg/kg}$ (Q3W x 2)

CR/PR/SD → Nivolumab Maintenance

PD → Immunotherapy resistance

PD → Nivolumab+Ipilimumab "Boost" 1+2

PR = 12%
CR = 2.7%

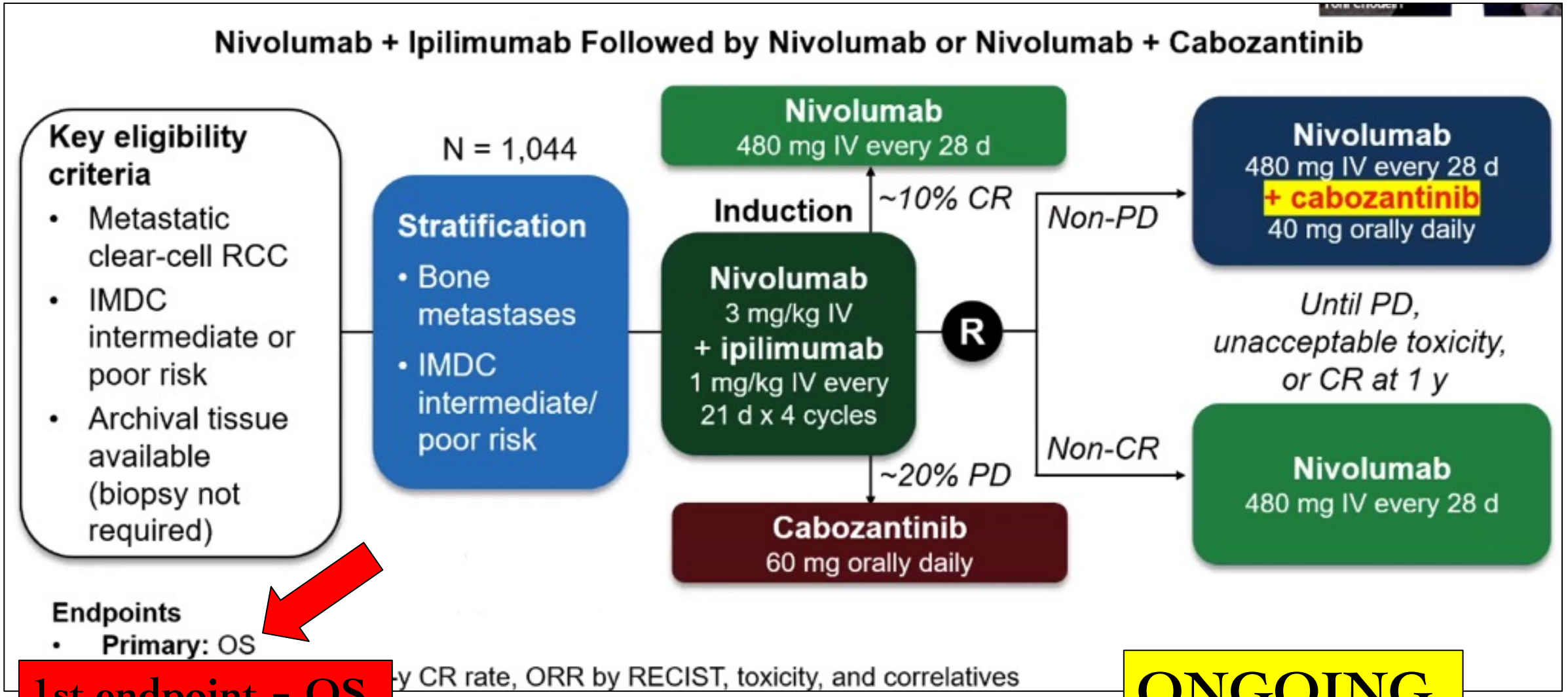
Primary endpoint: Overall Response Rate (ORR)
Secondary endpoints: PFS, OS, RR after Nivo+Ipi "B
Safety (TRAE), QoL (FKSI-19)

BARCELONA 2018 ESMO congress

PEDIGREE TRIAL

PHASE III

1044 pts

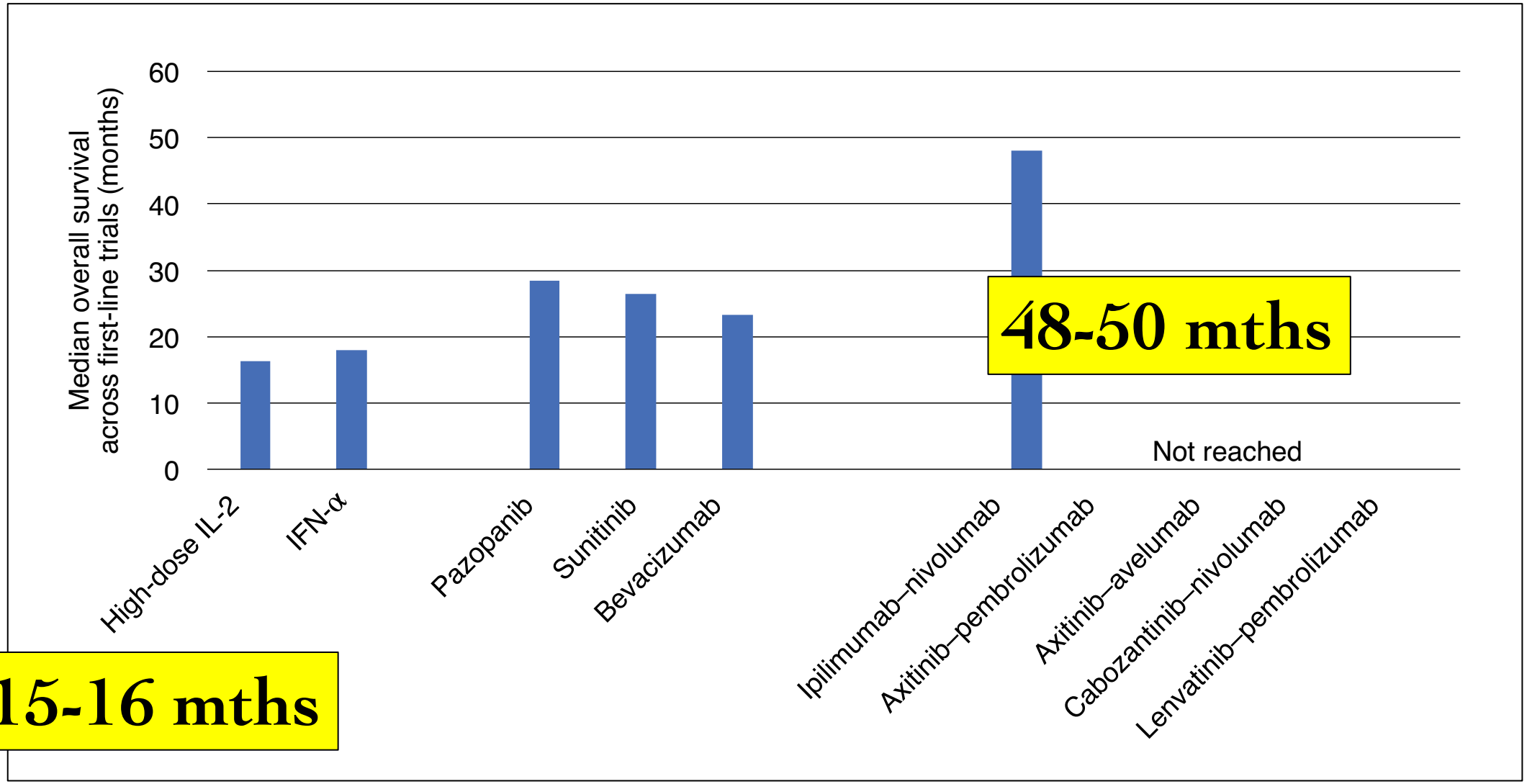


1st endpoint = OS

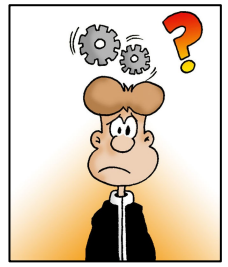
ONGOING

CONCLUSIONS

SPECTACULAR IMPROVEMENTS IN OS !!!



WHAT IS THE BEST CANDIDATE FOR IO+IO ???

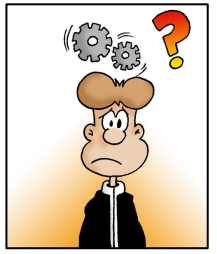


1. Particularly relevant with sarcomatoïd component…

2. Cardiac contra-indication

3.
- Without rapid progression
- When the primary goal is CURE
- Only chance to use IPILIMUMAB

WHAT IS THE BEST CANDIDATE FOR IO+TKI ???



1

Particularly relevant in anatomical sites where tumor growth may lead to adverse consequences (spinal canal; mediastinum;…)

2

- Particularly relevant in patients with
- aggressive disease
- high tumor burden and symptomatic patients
- with need rapid tumor shrinkage

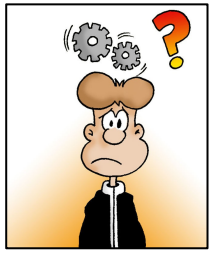
3 Contra-indication to corticosteroids (allergy; not-well controlled diabetes)

4 Brain metastases (especially with CABOZANTINIB)

5 Papillary histology

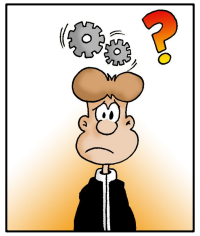
6 Patients with glandular (pancreas, adrenal, thyroid,…) metastases

WHAT IS THE BEST CANDIDATE FOR BONE METASTASES ???



INCIDENCE	20-24%
OUTCOMES	CABO + NIVO ?
ONJ : DENO + TKI	11-17%

BENEFITS OF INTENSIFICATION WITH « TRIPLET » ???



CHECKMATE 9ER TRIAL

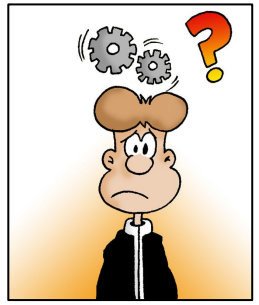
Grade 3-4 = 73-84% !!!

COSMIC TRIAL

- 1st endpoint met : PFS = HR 0.73
- Intermediate : PFS = HR 0.63
- Poor : PFS = NS ➔ ???
- ORR = 42% vs 36% ➔ not so impressive (excess of toxicity? No adequate exposure ?)
- OS = not yet mature

NOT a SoC !!!

WHAT IS THE BEST CANDIDATE FOR FAVORABLE IMDC RISK GROUP ???

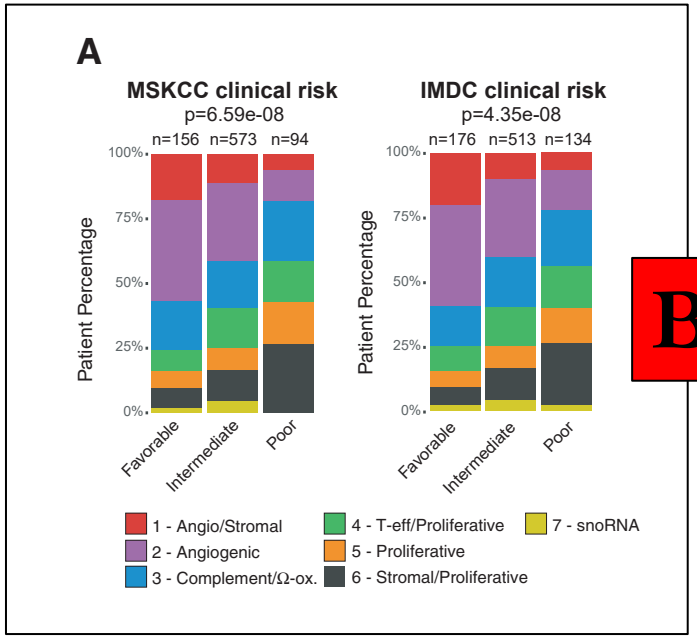


OS / 4 PHASE III RCTs

HR = NS

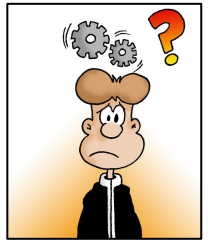
BELGIUM REIMBURSMENT

PEMB + AXI
NIVO + CABO



BIOMARKERS !!!

STILL PLACE FOR TKI MONOTHERAPY ???

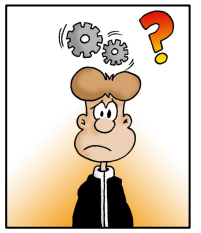


- significant comorbidities = immunosuppressed transplant recipients; severe autoimmune diseases
- unable to tolerate the added toxicity associated with combinaison (elderly and unfit)

- Clearly defined angiogenic profile
- Very favorable risk group ?

BIOMARKERS !!!

WHAT ABOUT TAILORED APPROACH ??



OMNIVORE TRIAL

HCRN GU16-260 TRIAL

TITAN TRIAL

Very low PR (4-12%)
Very rare CR (0-2.7%)
After « boost » by IPILUMIMAB

NOT a SoC !!!

PEDIGREE TRIAL

Ongoing !!!

TREATMENT SELECTION = complex and involves factors beyond IMDC score

DISEASE FACTORS

IMDC score
Tumor/symptom burden
Metastases`speed of response needed

PATIENT FACTORS

Age and lifestyle
Performance status
Comorbidities
Concomitant medications
Treatment preferences

TREATMENT FACTORS

Treatment access
Receipt of prior therapy
Efficacy/ safety/ HRQoL data

BIOMARKERS

There are currently
No biomarkers

BIONIKK TRIAL | PHASE II | 202 pts | mFU= 18 mths

BIONIKK (NCT02960906)

Metastatic Renal Cell Carcinoma
- Clear cell histology (translocation carcinoma allowed)
- Previously untreated in metastatic setting
- ECOG-PS≤2
- Available frozen tumor tissue

Determination of molecular group
(RT-qPCR)
ccrcc1-4
(35-gene signature)
<15days

1 → R → A
4 → R → B
2 → R → C
3 → R

Nivolumab 240mg IV every 2 weeks

Nivolumab IV 3 mg/kg + **Ipilimumab IV** 1 mg/kg every 3 weeks for 4 doses followed by **Nivolumab** IV 240 mg every 2 weeks

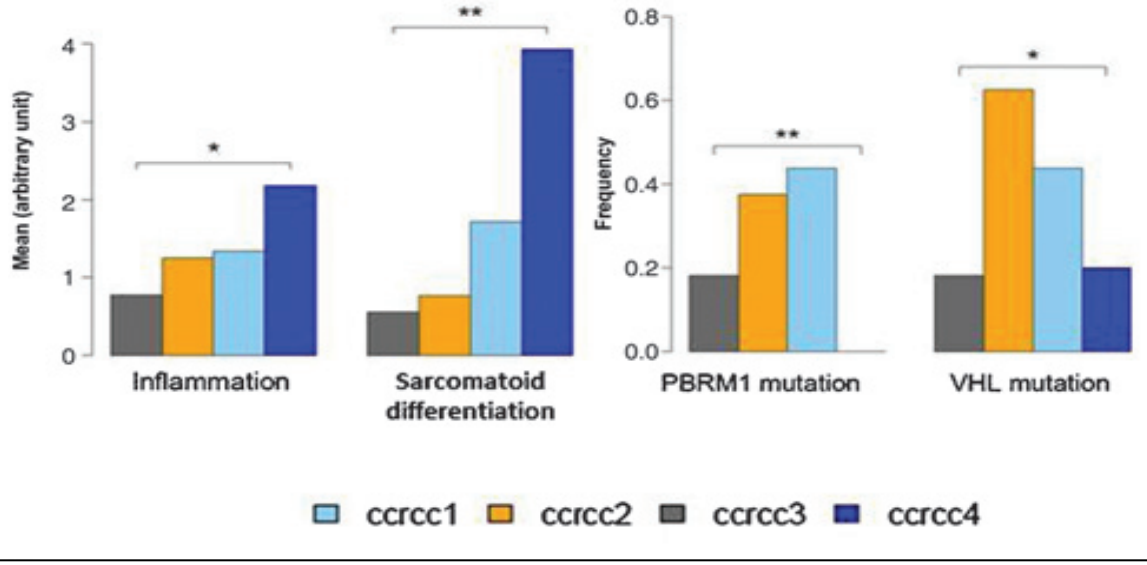
TKI (sunitinib or pazopanib)

Treat until RECIST 1.1-defined progression, death, unacceptable toxicity or end of study (18months)

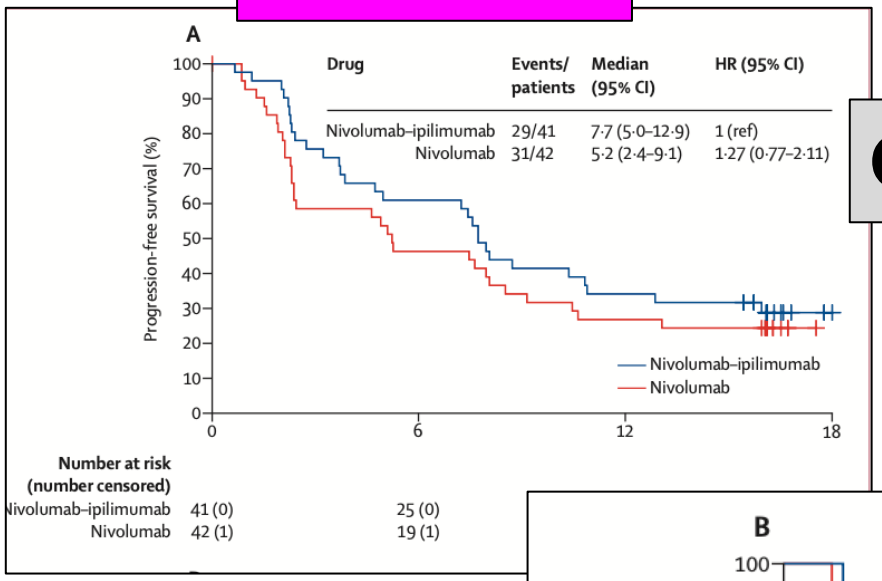
Non-comparative, per molecular-group randomized phase II trial

First step in tailoring treatment on the basis of tumour molecular phenotype !!!

CCRCC1 = 42% (immune-low)
CCRCC2 = 37%(angio-high)
CCRCC3 = 5% (normal-like)
CCRCC4 = 17% (immunoe-high)

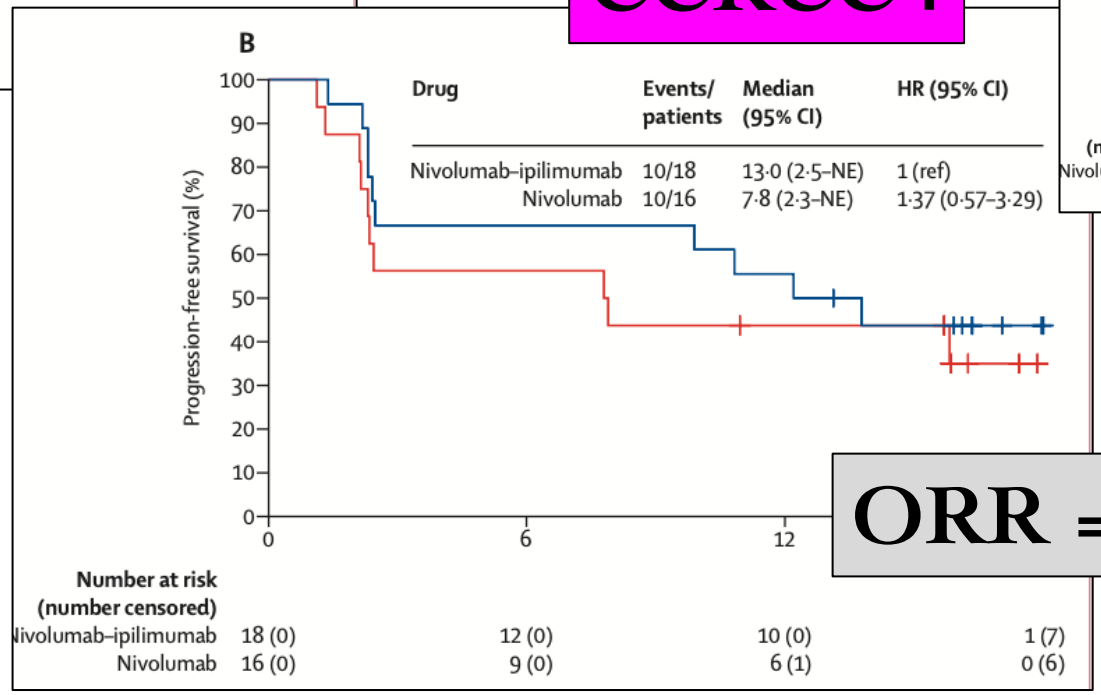


CCRCC1



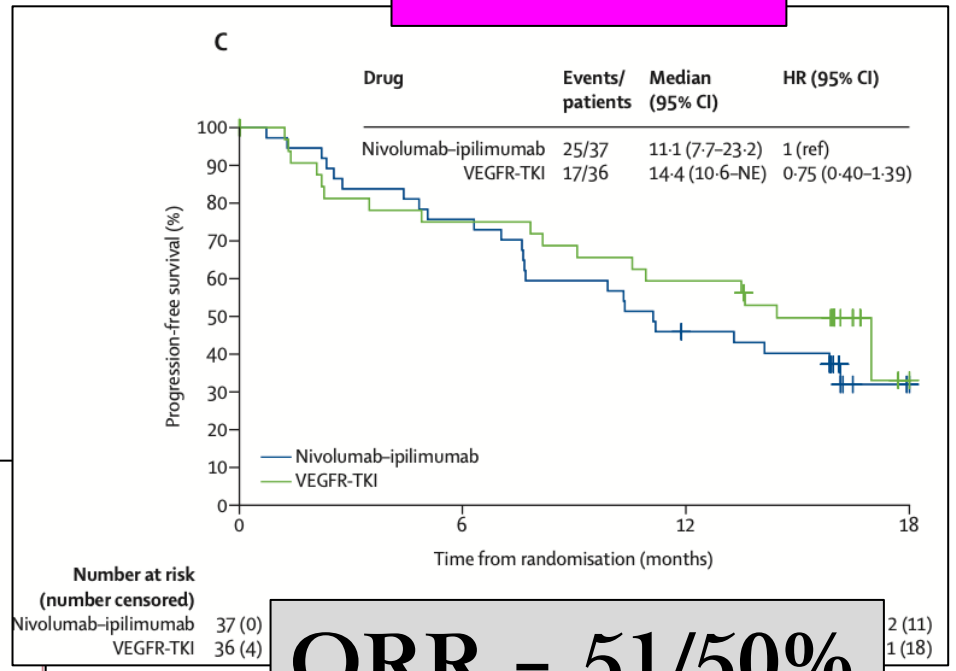
ORR = 39/29%

CCRCC4



ORR = 50/44%

CCRCC2



ORR = 51/50%

PIPELINE FOR RCC

Drug	Company	Mechanism of action	Highest phase
MK-1308A	Merck & Co.	PD1 and CTLA4 inhibitor	Phase III
Toripalimab (Tuoyi)	Shanghai Junshi Biosciences	PD1 inhibitor	Phase III
Durvalumab (Imfinzi)	AstraZeneca	PDL1 inhibitor	Phase III
Tremelimumab (Imjudo)	AstraZeneca	CTLA4 inhibitor	Phase III
Savolitinib (Orpathys)	AstraZeneca	MET inhibitor	Phase III
Zanzalintinib	Exelixis	Multitarget TKI	Phase III
Abexinostat	Xynomic Pharmaceuticals	HDAC inhibitor	Phase III
Batiraxcept	Aravive	GAS6-AXL pathway inhibitor	Phase II
NKT2152	NiKang Therapeutics	HIF2α inhibitor	Phase II
DFF332	Novartis	HIF2α inhibitor	Phase I
AB521	Arcus Biosciences	HIF2α inhibitor	Phase I
ALLO-316	Allogene Therapeutics	Anti-CD70 allogeneic CAR-T cell therapy	Phase I
CTX-131	CRISPR Therapeutics	Anti-CD70 allogeneic CAR-T cell therapy	Phase I
Ciforadenant	Corvus Pharmaceuticals	Adenosine A2A receptor antagonist	Phase II
XmAb819	Xencor	ENPP3 × CD3 bispecific antibody	Phase I

CAR, chimeric antigen receptor; CD, cluster of differentiation; CTLA4, cytotoxic T-lymphocyte associated protein 4; ENPP3, ectonucleotide pyrophosphatase/phosphodiesterase family member 3; GAS6, growth arrest-specific protein 6; HDAC, histone deacetylase; HIF2α, hypoxia-inducible factor 2α; MET, mesenchymal-epithelial transition factor; PD1, programmed cell death protein 1; PDL1, programmed death ligand 1; TKI, tyrosine kinase inhibitor.

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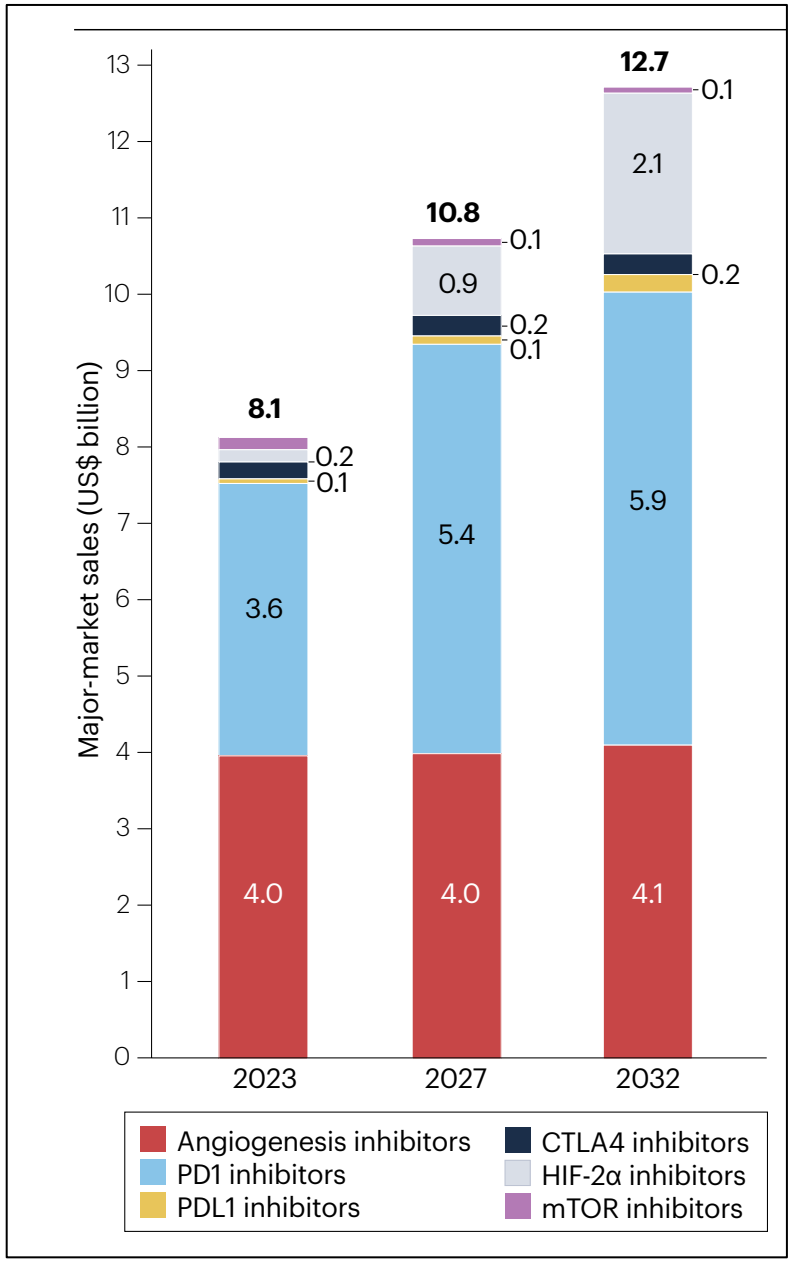
RCC DRUG MARKET

MAJOR-MARKET SALES



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