GUARD CONSORTIUM

How to Treat Patients with RCC Who Relapse After Adjuvant Treatment

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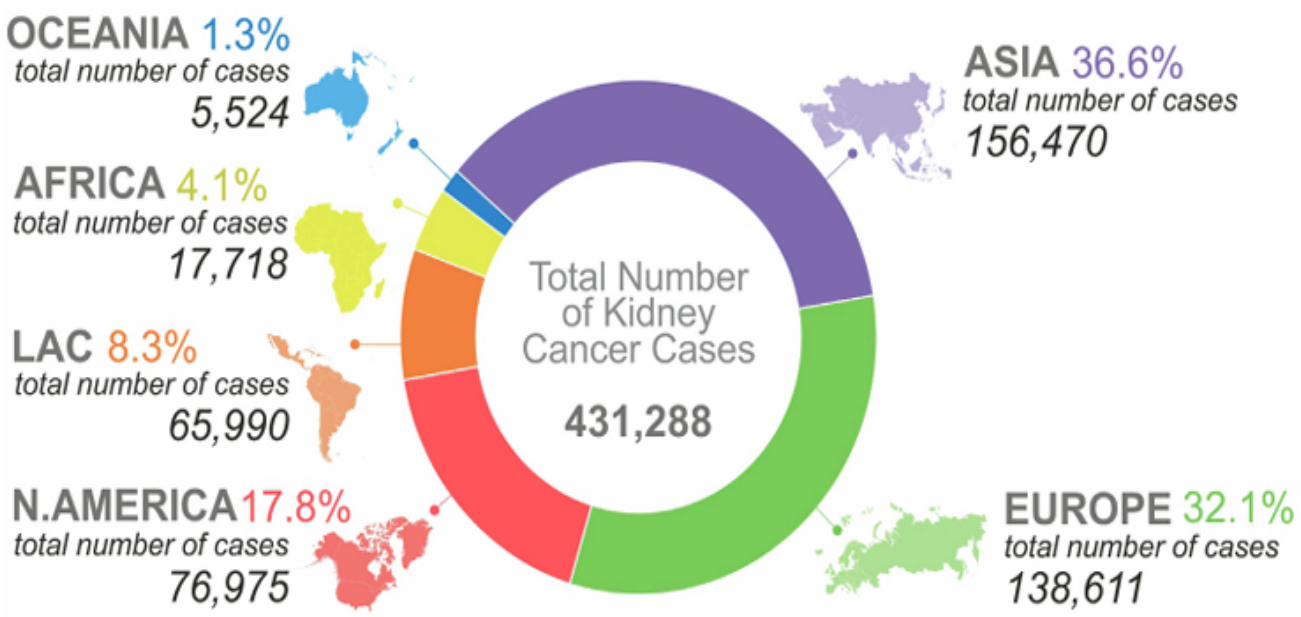
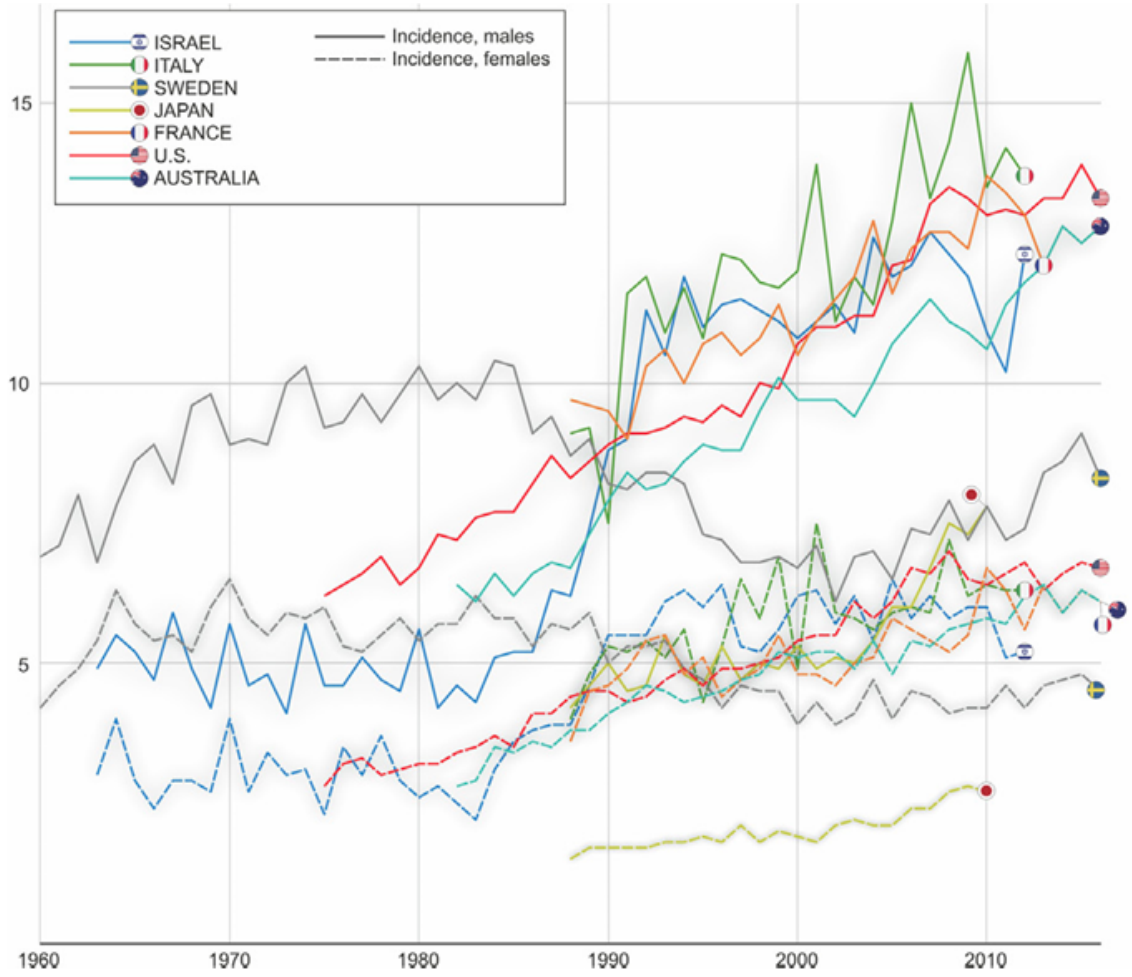
Disclosures

Consultant: Astellas; AstraZeneca; Eisai; Exelixis; Janssen, EMD Serono; Dendreon; Pfizer, Seattle Genetics, BMS, Bayer, Guardant Health; Caris Life Sciences, Novartis
Contracted Research: Merck, Caris Life Sciences, ESSA Pharma
Research Grant: BlueEarth Diagnostics, Merck, Exelixis
Speaker's Bureau: Astellas

Renal Cell Carcinoma Around the Globe





World Health Organization;
Bukavina et al, Eur Uro 2022

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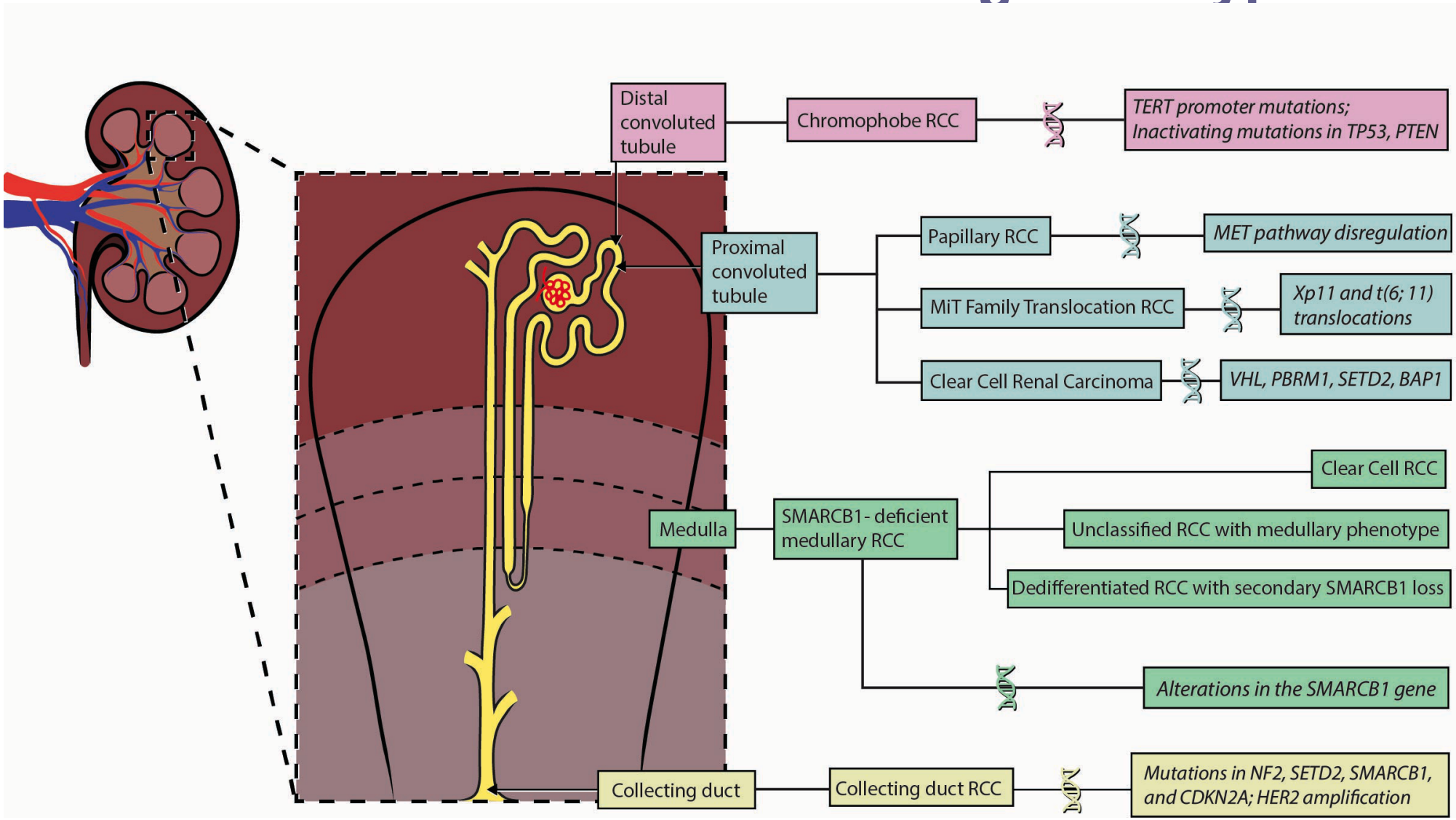
Renal Cell Carcinoma Histologic Subtypes

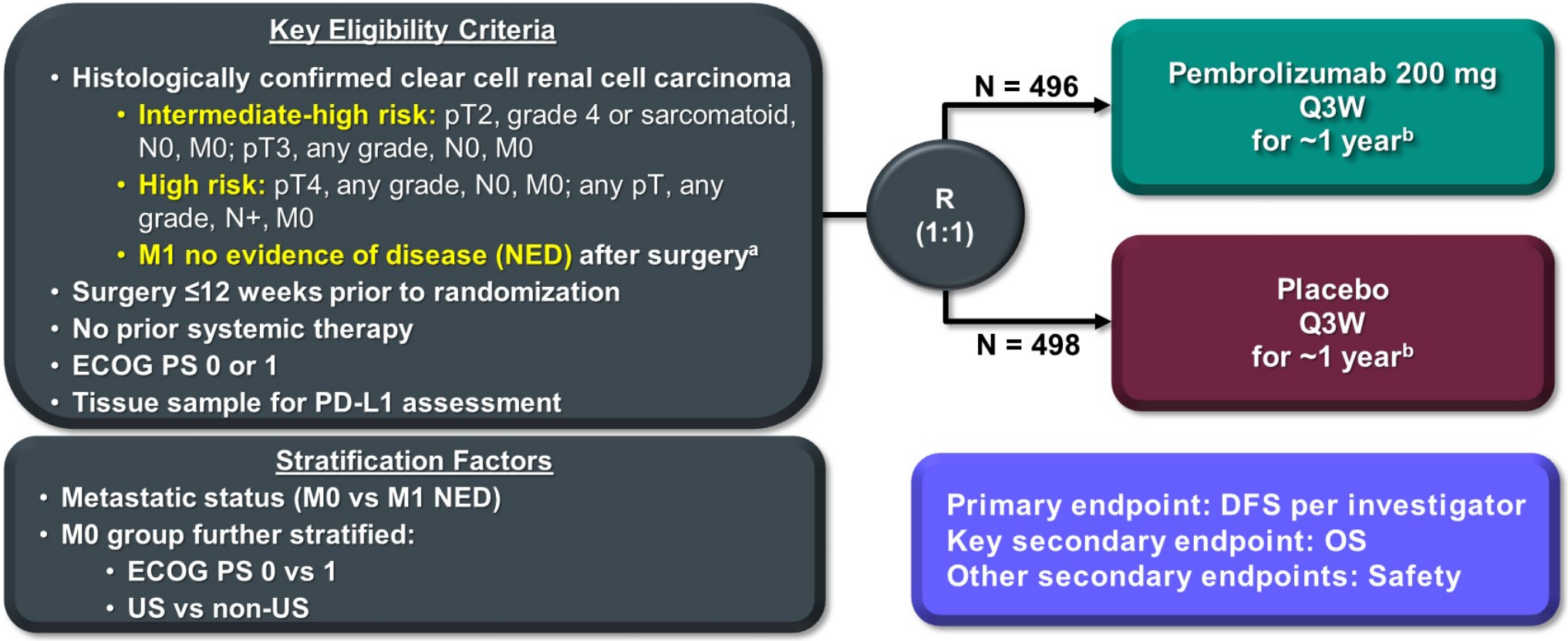


Different Models Predict Risk of Recurrence

- ~50% of post-nephrectomy patients with high-risk features will eventually recur;
- Factors such as disease stage, size, nuclear grade, regional LN involvement are associated with disease recurrence and survival.

Model	RCC subtype	Factors
Kattan, Kattan M et al, J Urol 2001	Any	TNM, tumor size, histology, symptoms
SSIGN/Mayo, Frank I et al, J Urol 2002	Clear cell	TNM, tumor size, grade, tumor necrosis
Leibovich, Leibovich et al, Cancer 2003	Clear cell	TNM, N+, size, grade, tumor necrosis
UCLA/UISS, Patard JJ et al, JCO 2004	Any	TNM, grade, ECOG PS
MSKCC, Sorbellini et al, J Urol 2005	Clear cell	TNM, tumor size, grade, tumor necrosis, vascular invasion, symptoms
Karakiewicz, Karakiewicz et al, JCO 2007	Any	TNM, tumor size, grade, histology, age, symptoms
GRANT, Buti S et al, ESMO 2017	Any	Grade, age, Nodes, tumor size
VENUSS, Klatte T et al, BMC Med 2019	Papillary	TNM, Venous tumor thrombus, grade, size

KEYNOTE-564 Study Design



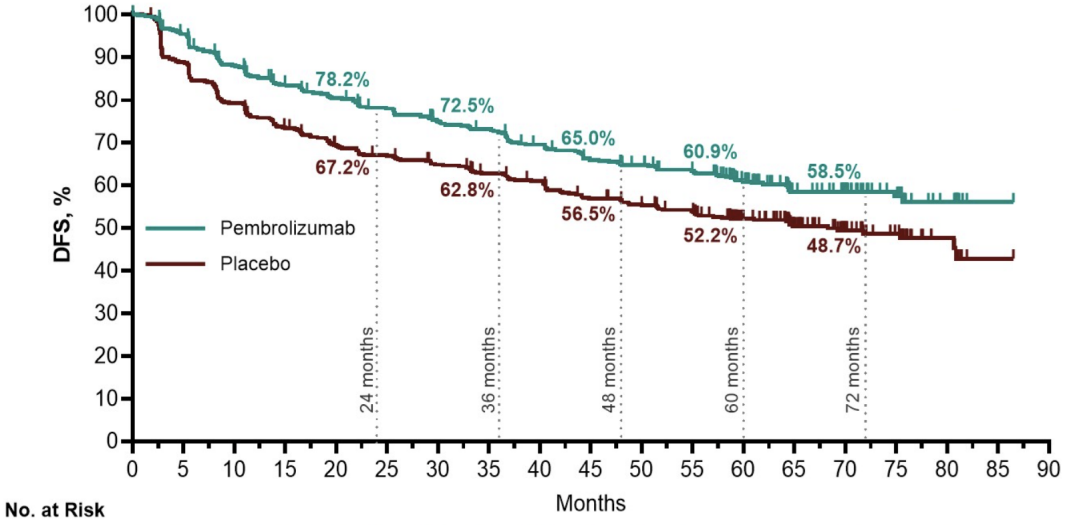
- Median (range) time from randomization to cutoff: 30.1 (20.8–47.5) months

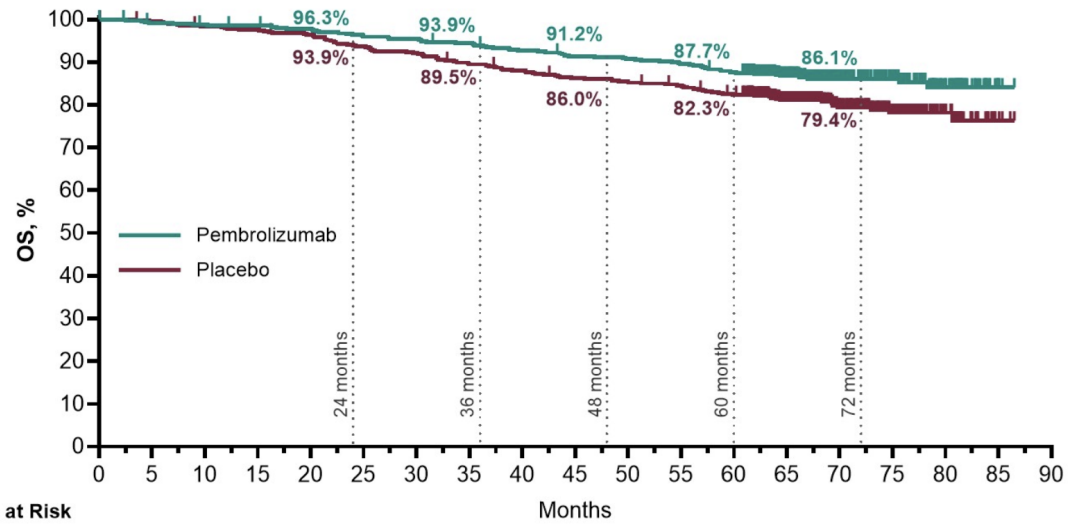
Q3W, every 3 weeks.
[a]M1 NED: no evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy; [b]≤17 cycles of treatment were equivalent to ~1 year.
Data cutoff date: June 14, 2021.

Choueiri TK, et al. *N Engl J Med*. 2021; 385(8):683-694.
Powles T, et al. *Lancet Oncol*. 2022;23(9):1133-1144.

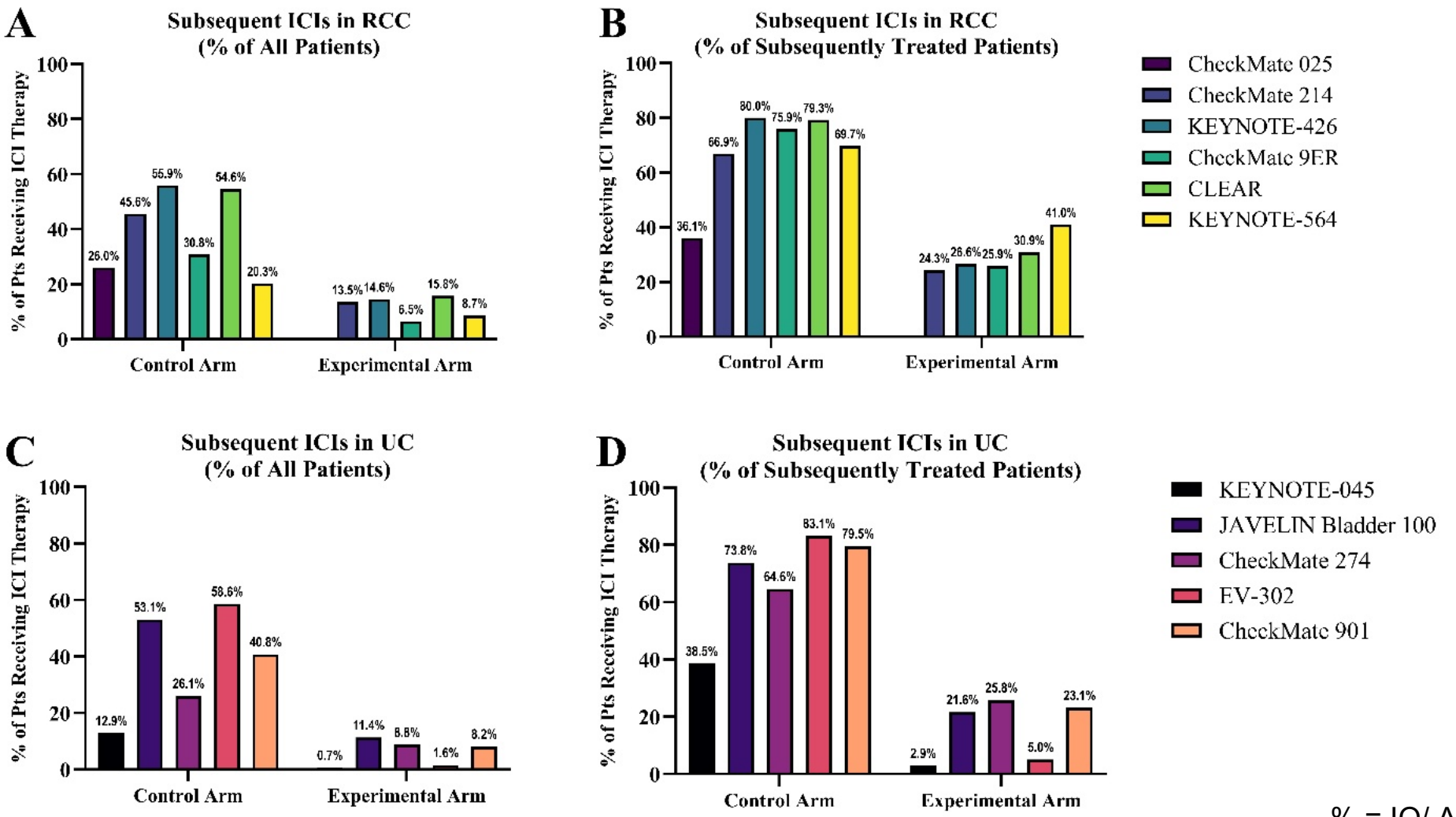
KEYNOTE-564 DFS & OS benefit Not By Chance!

	June 2021	Sep 2022	Jan 2024	Sep 24
Analysis	1st	2nd	3rd	4rd
Median follow up, months	24.1	30	57.2	69.5
Disease free survival (HR, CI 95%), p-value	0.68 *P=0.0010*	0.63 *P<0.0001*	0.72 NE	0.71 NR
DFS events	109 vs 151	114 vs 169	174 vs 224	188 vs 241
Overall survival (HR, CI 95%)	0.54 *P=0.0164 (int)*	0.52 *P=0.0048 (int)*	0.62 ***P=0.002****	***0.66*** ***NR***
OS events	18 vs 33	23 vs 43	55 vs 86	68 vs 99





Subsequent ICI data (any line) for the included registrational phase 3 trials



% = IO/ Any systemic tx

Grier et al, Eur Urol Open Science 2025 (*in revision*)

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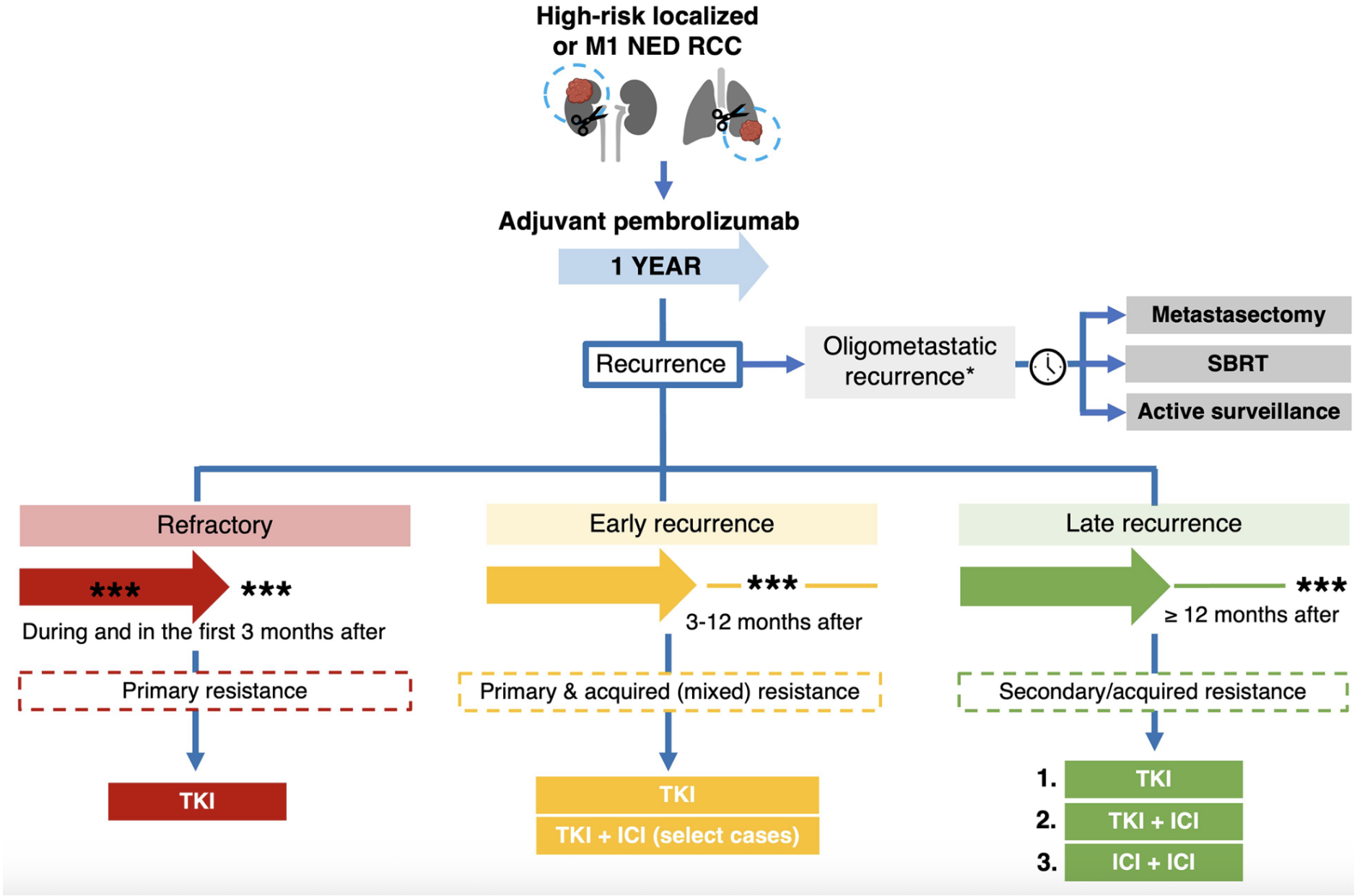
High-risk localized
or M1 NED RCC
Adjuvant pembrolizumab
1 YEAR
Recurrence
Oligometastatic recurrence*
Metastasectomy
SBRT
Active surveillance
Refractory
***
***
During and in the first 3 months after
Primary resistance
TKI
Early recurrence
***
3-12 months after
Primary & acquired (mixed) resistance
TKI
TKI + ICI (select cases)
Late recurrence
***
≥ 12 months after
Secondary/acquired resistance
1. TKI
2. TKI + ICI
3. ICI + ICI

Front line treatment options in mRCC

First: Do I need to start systemic treatment?

Active surveillance is an option for selected patients

What do I do with a primary tumor?

Surgery? External beam radiation therapy?

Upfront vs deferred nephrectomy

PROBE (SWOG)
SAMURAI (NRG)

mRCC, metastatic renal cell carcinoma
Slide courtesy of Dr P Barata

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Treatment Upon Progression: How Many Need It / How Many Get It

	Participants with Documented Recurrence, n	
	Pembrolizumab (n = 171)	Placebo (n = 226)
Systemic therapy only	73 (42.7%)	100 (44.2%)
Systemic + surgery/radiation therapy	37 (21.6%)	54 (23.9%)
Surgery/radiation therapy only	33 (19.3%)	30 (13.3%)
No subsequent therapy reported[a]	28 (16.4%)	42 (18.6%)
VEGF/VEGFR inhibitor[b]	101 (59.1%)	133 (58.8%)
Anti–PD-(L)1 therapy[b]	49 (28.7%)	109 (48.2%)

Front Line Treatment Options in Metastatic RCC

IO-IO

- Nivolumab + Ipilimumab

IO-VEGF

- Pembrolizumab + Axitinib
- Avelumab + Axitinib
- Nivolumab + Cabozantinib
- Pembrolizumab + Lenvatinib

VEGF

- Cabozantinib
- Sunitinib
- Pazopanib

NCCN Guidelines Version 3.2025
Kidney Cancer

PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV OR RELAPSED DISEASE

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY)

Immuno-oncology (IO) Therapy History Status	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Prior IO Therapy	• None	• Axitinib • Belzutifan[c] • Cabozantinib • Everolimus + lenvatinib • Tivozanib[d]	• Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Everolimus • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Bevacizumab[e] (category 2B) • Axitinib + avelumab[b] (category 3)

FDA–approved indications

Belzutifan	Advanced RCC following a PD-(L)1 inhibitor and a VEGF TKI
Tivozanib	Relapsed or refractory advanced RCC following ≥ 2 prior systemic therapies

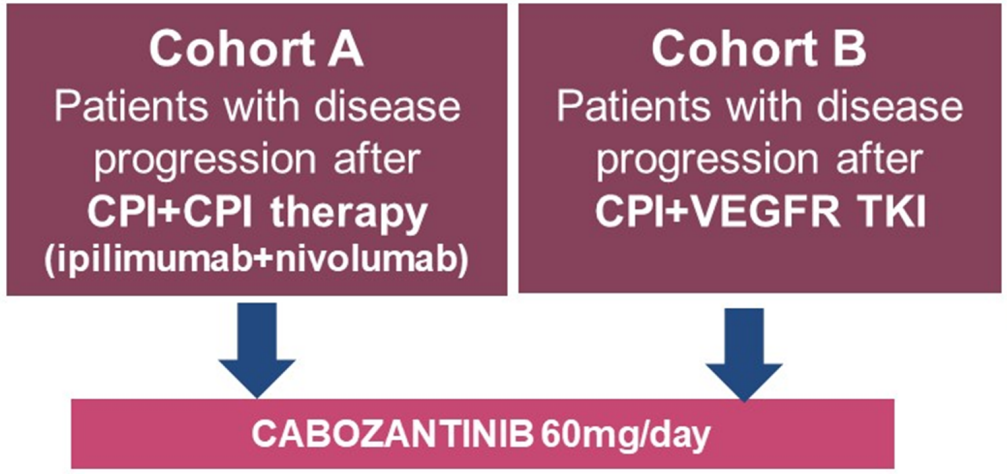
IO, immunotherapy; VEGF, vascular endothelial growth factor.

Treatment	Study/Trial Design	N	Prior Therapies	Overall Survival	Objective Response Rate	Progression Free Survival or TTF*	Grade 3 or 4 Toxicity
Cabozantinib	Phase III vs. everolimus, METEOR	658 (330 vs. 328)	1+TKI (5% prior ICI)	21.4 vs. 16.5 months (HR 0.66)	17% vs. 3%	7.4 vs. 3.9 months (HR 0.51)	71% vs 60%
	Phase II control arm, CANTATA	223	TKI or dual ICI		28%	9.2 months	79%
	Phase II, BREAKPOINT NCT03744585	48	Adjuvant or first line ICI		43%	9.3 months	34%
Lenvatinib + Everolimus	Phase II vs. everolimus, NCT01136733	91 (51 vs. 50)	TKI	25.5 vs. 15.4 months (HR 0.51)	43% vs. 6% (RR 7.2)	14.6 vs. 5.5 months (HR 0.40)	71% vs. 50%
Tivozanib	Phase III vs. Sorafenib, TIVO-3	350 (175 vs. 175)	2+ systemic therapies	At 22.8 months, HR 0.89, (CI 0.70-1.14)	18% vs. 8%	5.6 vs. 3.9 months (HR 0.73)	11% vs. 10%
Axitinib	Phase III vs. Sorafenib, AXIS	723 (361 vs. 362)	Sunitinib or other *	20.1 vs. 19.2 months (HR 0.969)	8.3 vs. 5.7 months (HR 0.66)	23% vs. 12%	17% vs. 12% HTN*
Belzutifan	Phase III vs. everolimus, Litespark-005	746 (374 vs 372)	1-3 prior, 1 TKI + 1 PD(L)1	21 vs. 21.4 months (HR 0.87)	21.9% vs 3.5%	5.6 vs 5.6 months (0.75)	

*TTF—time to treatment failure; D/C—discontinue; SD—stable disease; HTN—hypertension.**Cytokines, bevacizumab with interferon, or temsirolimus.

CaboPoint: Trial Design

- Ongoing phase 2, open-label study conducted in Austria, France, Germany, Netherlands, Spain, Switzerland, and the UK



Key inclusion criteria	Key exclusion criteria
• Histologically confirmed, advanced or metastatic RCC with a clear-cell component • Radiographic disease progression following CPI–CPI therapy or CPI in combination with VEGF-targeted therapy	• Previous use of cabozantinib • untreated brain or leptomeningeal metastases

Endpoints

Primary endpoint: ORR per RECIST v1.1 in cohort A, by **independent central review**

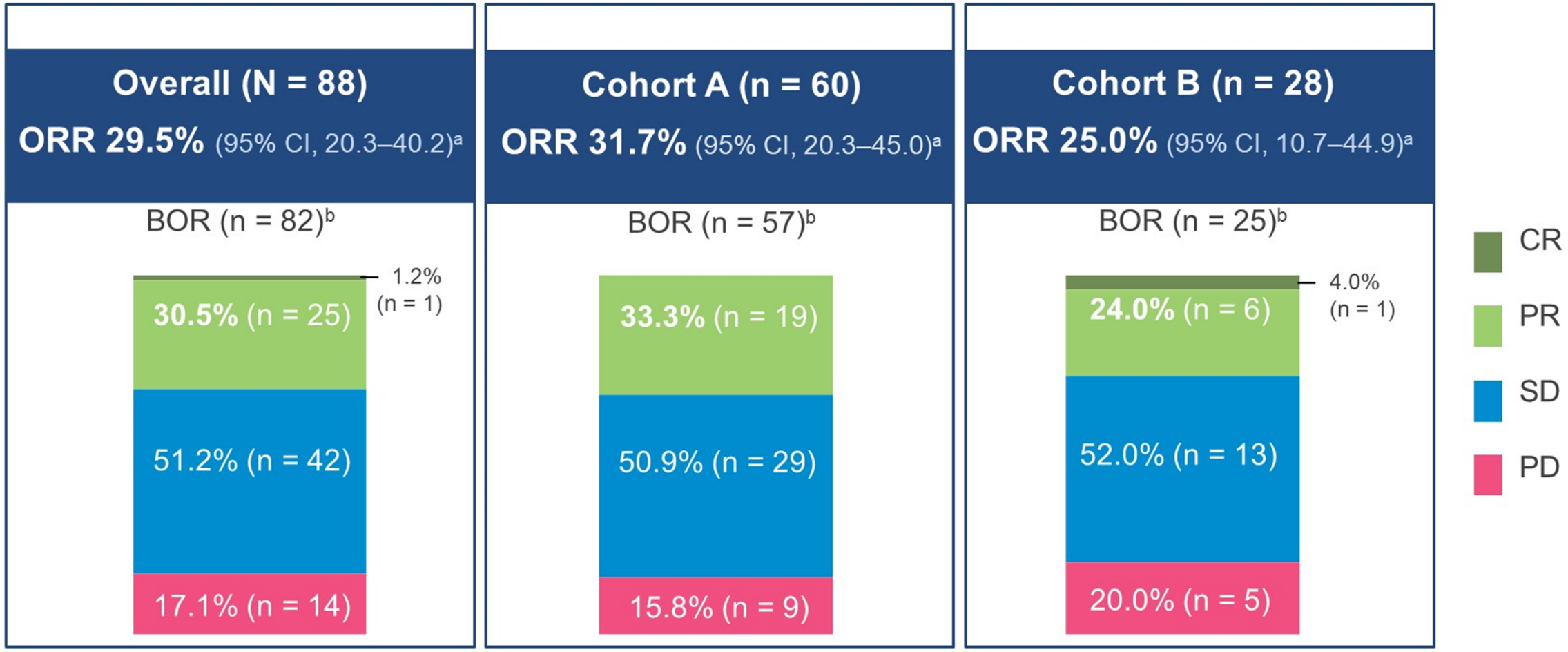
Secondary endpoints:

ORR in cohort B by independent central review; ORR for both cohorts by local investigator review; time to response[a]; duration of response[a]; disease control rate[a]; progression-free survival[a]; overall survival; change in disease-related symptoms; safety and tolerability

Laurence Albiges, ASCO GU 2023, #606

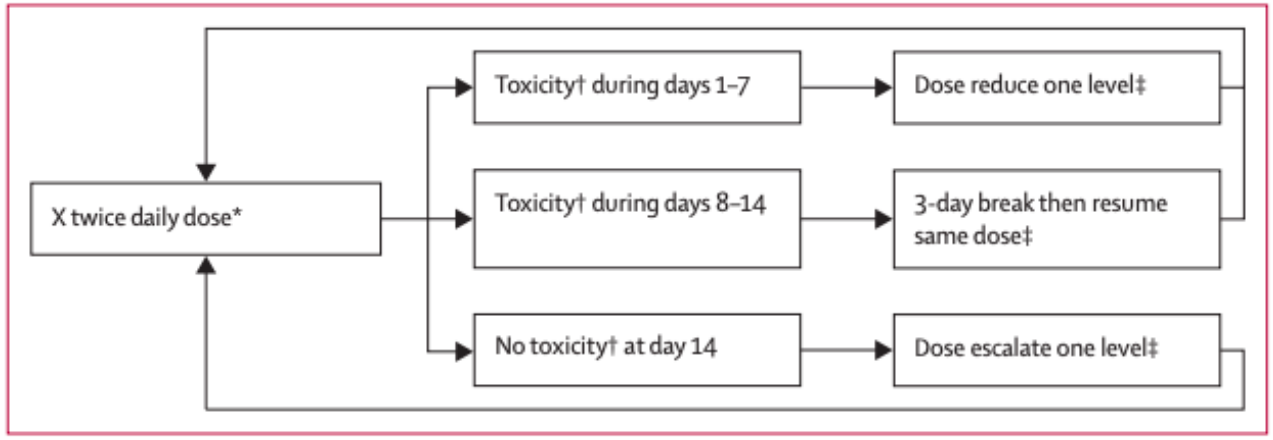
CaboPoint: Interim Efficacy (3 months analysis)

Cabozantinib demonstrated preliminary efficacy in patients with advanced RCC after progression on ICI-based combination therapy, irrespective of prior TKI exposure



Individualised axitinib regimen for patients with metastatic renal cell carcinoma after treatment with checkpoint inhibitors: a multicentre, single-arm, phase 2 study

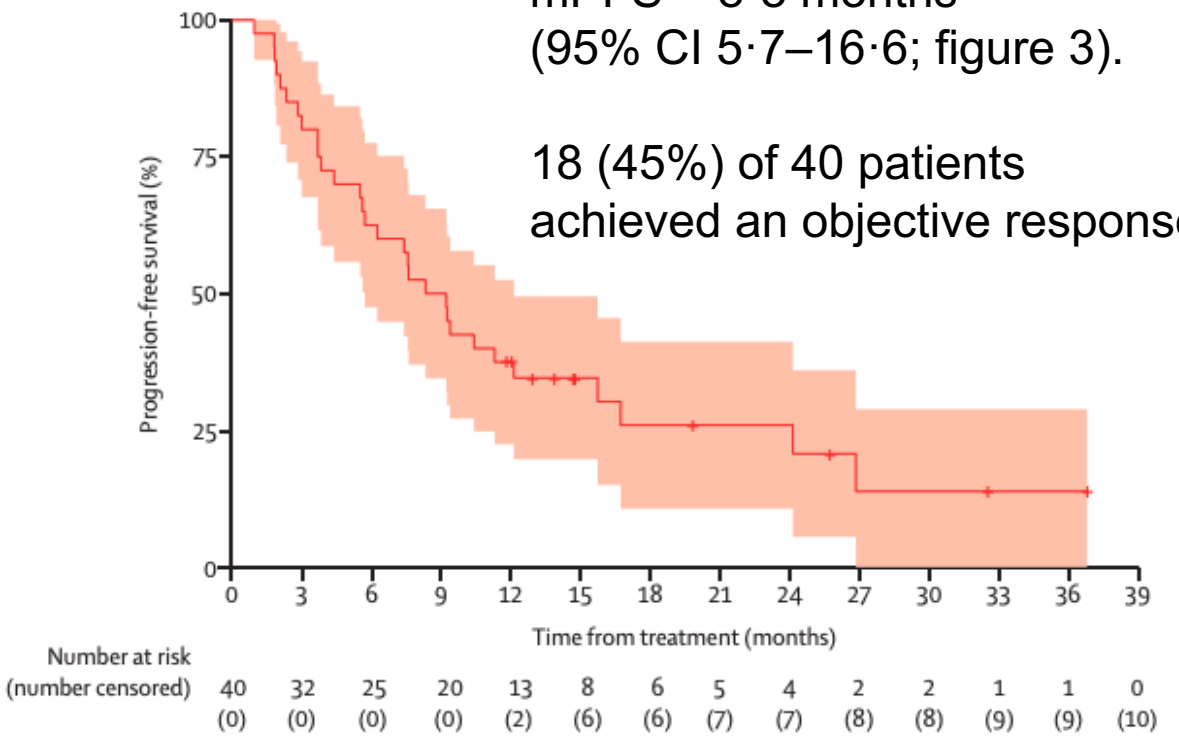
Moshe C Ornstein, Sumanta K Pal, Laura S Wood, Jackie M Tomer, Brian P Hobbs, Xuefei S Jia, Kimberly D Allman, Allison Martin, Thomas Olencki, Nancy B Davis, Timothy D Gilligan, Amir Mortazavi, W Kimryn Rathmell, Jorge A Garcia, Brian I Rini



N = 58 pts

mPFS = 8·8 months (95% CI 5·7–16·6; figure 3).

18 (45%) of 40 patients achieved an objective response



Is CTLA-4 Inhibitor active after prior PD(L)-1?

The role of NIVO + IPI (salvage/rescue)

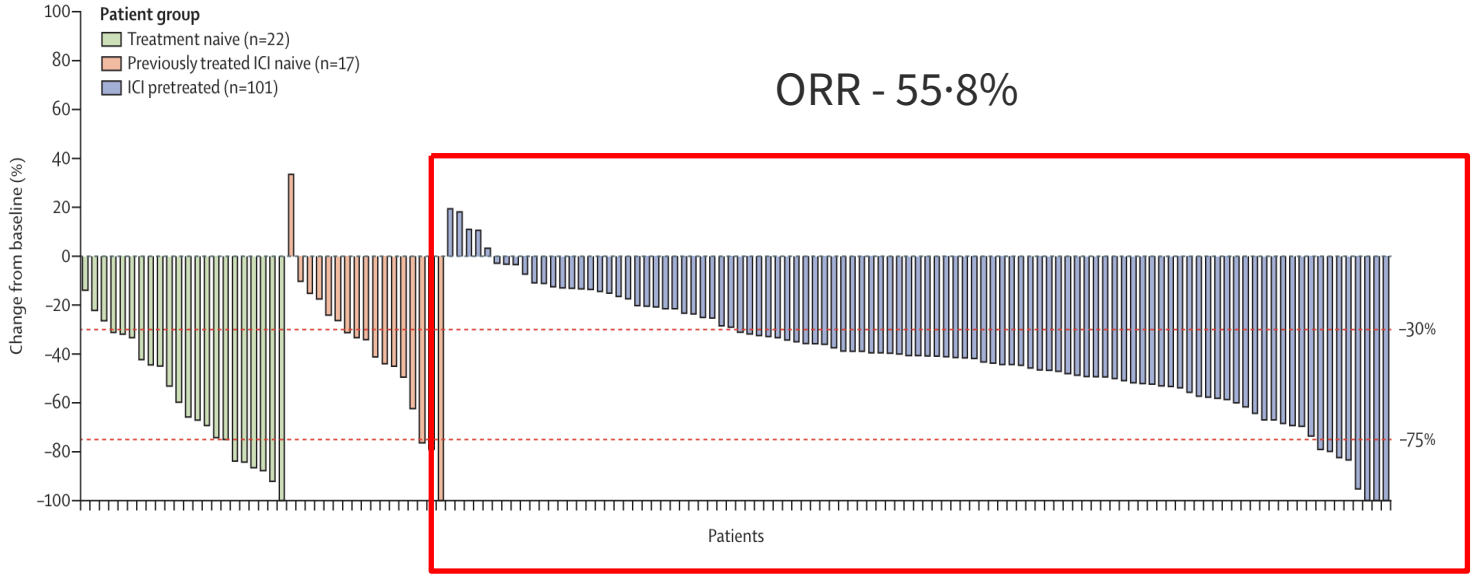
	HCRN GU16-260 ASCO 2020	OMNIVORE ASCO 2020	FRACTION ASCO 2020	TITAN RCC ESMO 2019	Salvage Ipi/Nivo (JCO 2020)
N	123	83	46	207	45
Prior TKI	No	Yes	Yes	Yes	Yes
Timing	Nivo→Ipi	Nivo→Ipi	Nivo+Ipi	Nivo→Ipi	I/N after prior IO
Ipi doses	4	2	4	4	4
ORR	13%	4%	15%	12%	20%
CR	0%	0%	0%	3%	0%

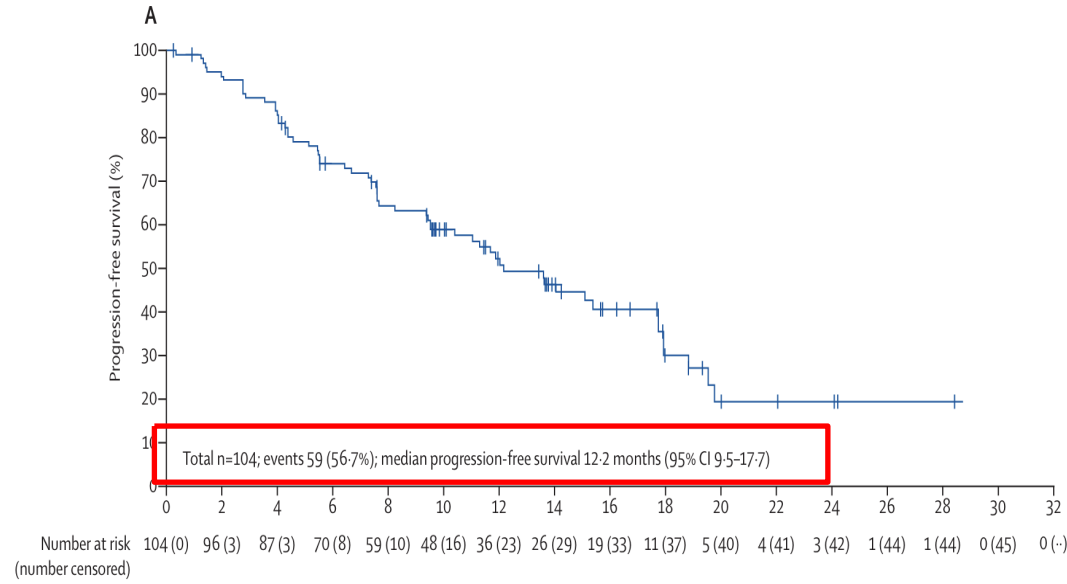
Nivo+ipi combo untreated ccRCC ORR 42%, CR 11% (Checkmate 214)

Is IO-TKI active after prior IO?

Study 111/KEYNOTE-146

N = 101 ICI-treated pts

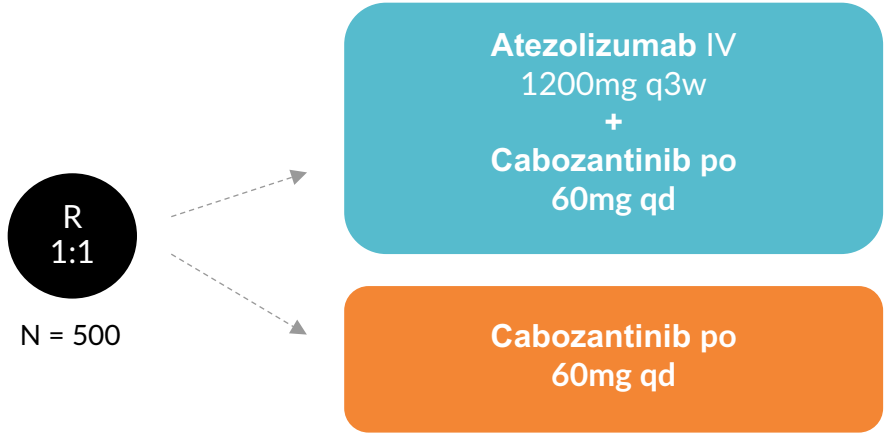




Salvage PD-(L)1 Inhibitor is not superior to TKI alone

CONTACT-03

- Histologically confirmed advanced, metastatic ccRCC or nccRCC
- Radiographic progression during or following ICI treatment



No crossover allowed

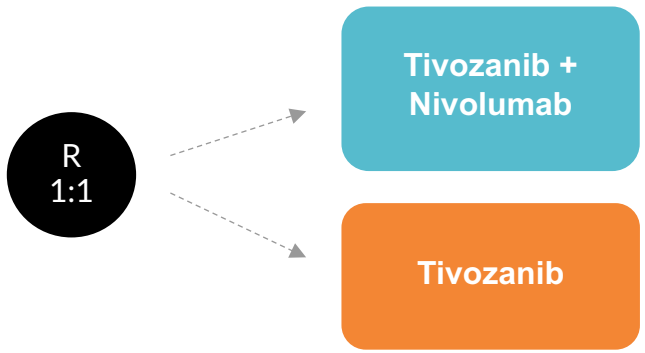
Negative Trial

Treatment until progression

- Primary endpoint: PFS, OS
- Secondary endpoint: PFS, ORR, DoR, Safety and Tolerability

TINIVO-2

- Histologically/cytologically confirmed recurrent/ metastatic RCC
- ECOG PS 0 or 1
- Progressed following immediate prior immunotherapy treatment in first or second line
- Stratified by IMDC and prior TKI



Negative Trial

Treatment until progression

- Primary endpoint: PFS
- Secondary endpoint: OS, ORR, DoR, Safety and Tolerability

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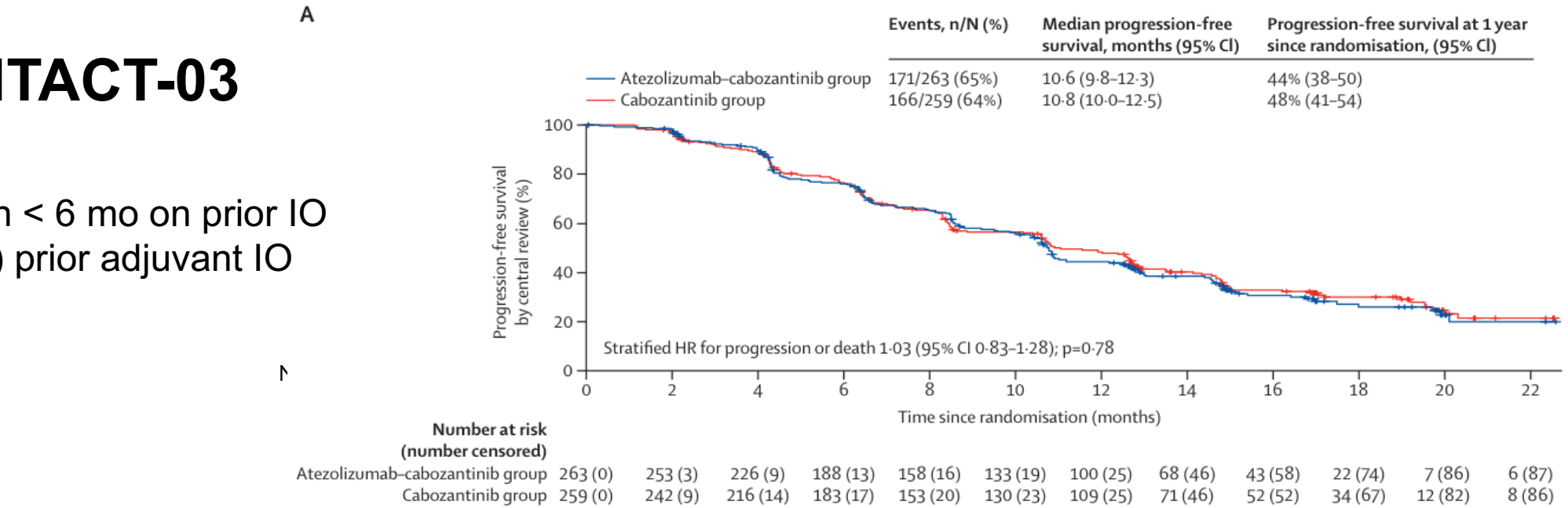
Salvage PD-(L)1 Inhibitor is not superior to TKI alone

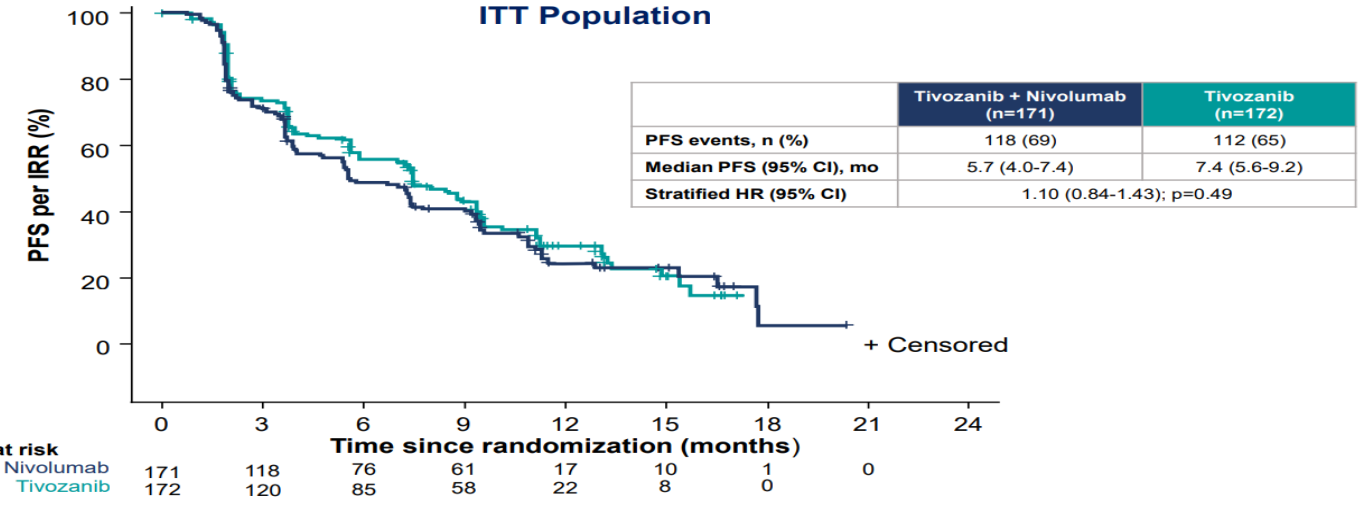
CONTACT-03

Progression < 6 mo on prior IO
< 1% (N=2) prior adjuvant IO



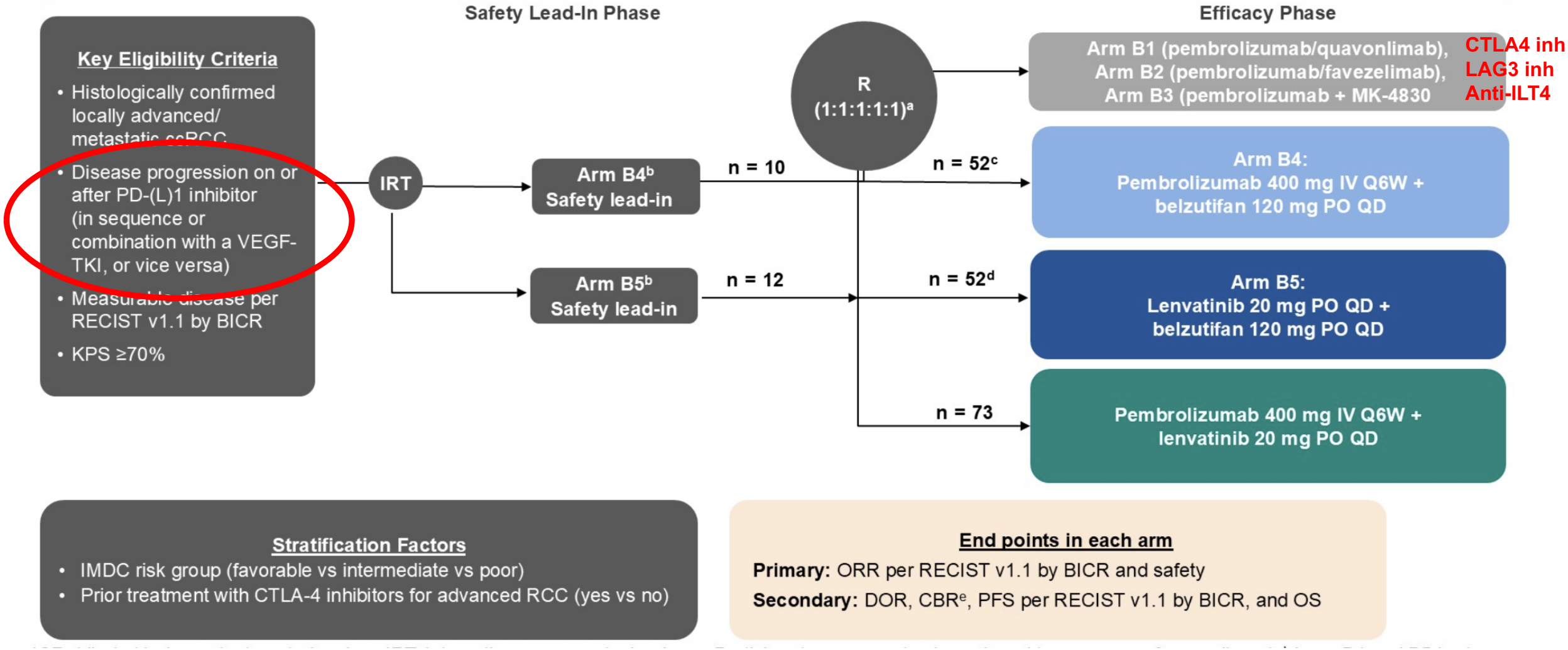
TINIVO-2

14% (N=47) prior adjuvant IO



Median follow-up was 11.8 months in the tivozanib + nivolumab cohort and 12.5 months in the tivozanib monotherapy arm

KEYMAKER-U03 Substudy 03B Study Design (NCT04626518)



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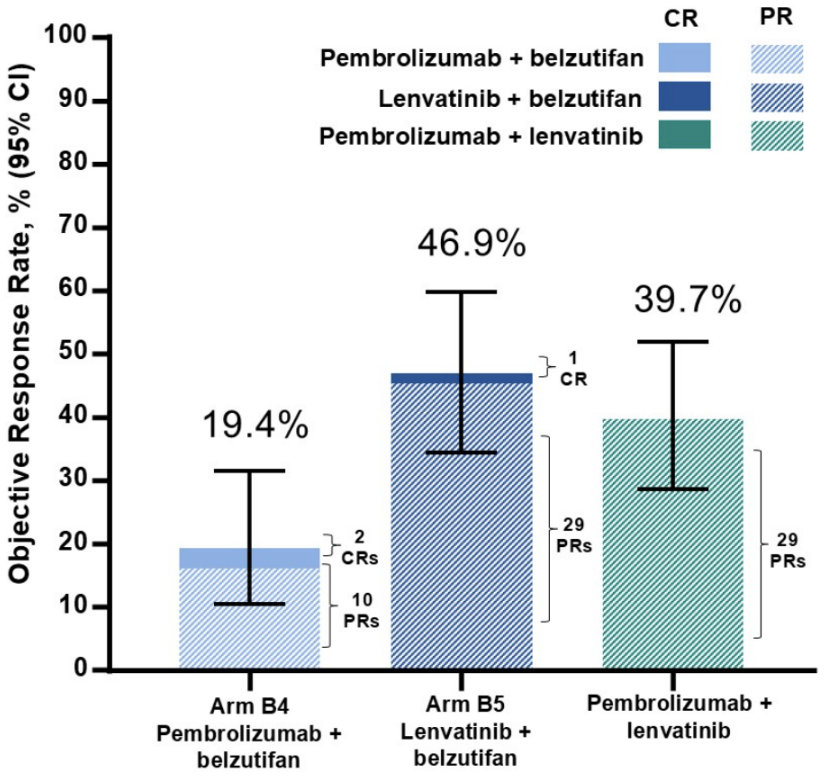
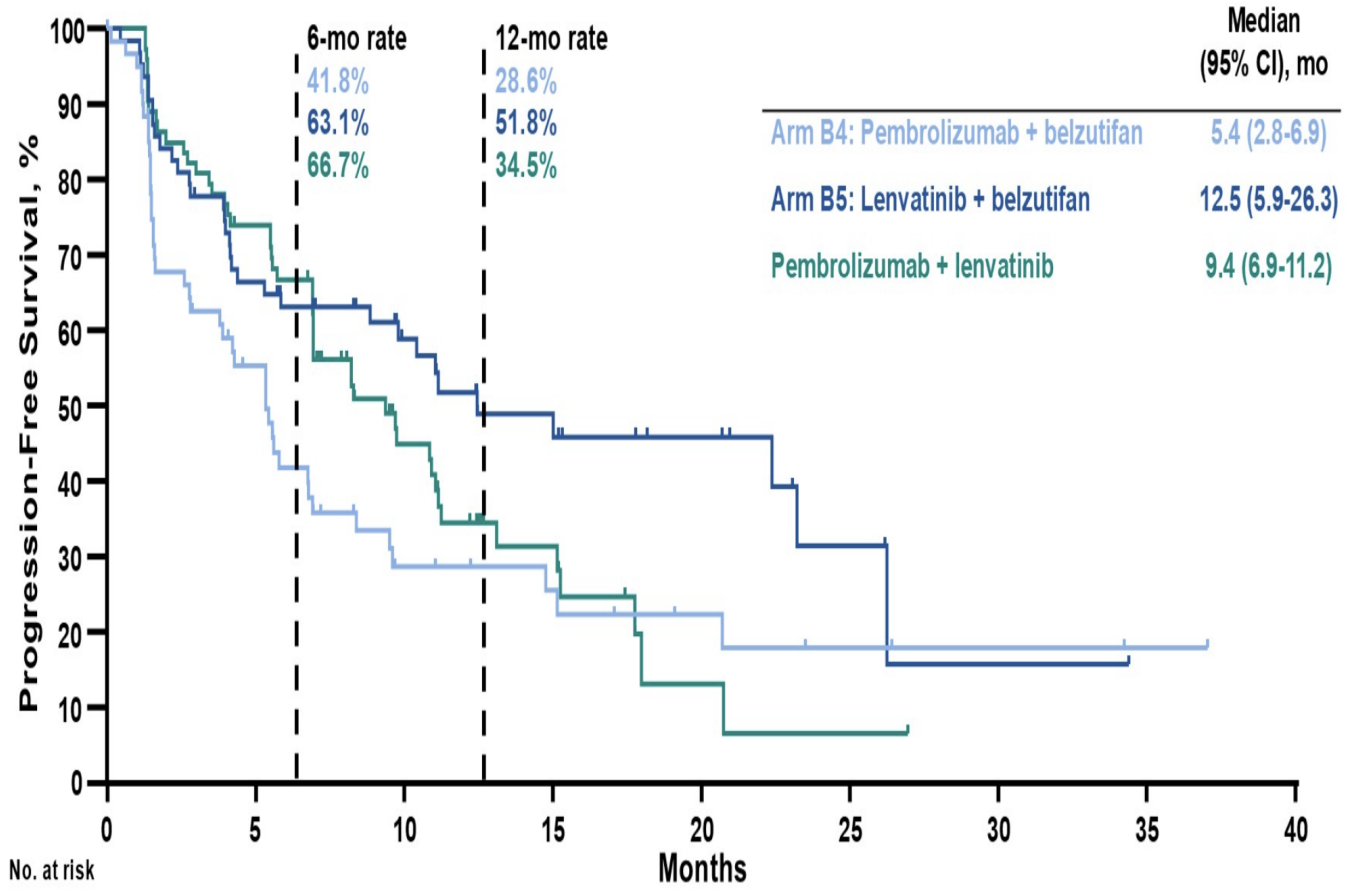
ORR and PFS for cohorts B4/B5/LP





Data cutoff date: March 22, 2024.

Current status of adjuvant immunotherapy and relapse management in renal cell carcinoma: Insights from a European Delphi study

Patients who relapse during or within 6 months of completing adjuvant ICI therapy	Are considered ICI-refractory
Focal therapies with curative intent for patients previously treated with adjuvant ICI therapy and have an oligometastatic recurrence	Should always be considered
Patients with ICI-refractory disease	Should receive targeted therapy without an ICI component; Or be considered for clinical trial inclusion
Patients who experience recurrence more than 12 months after completing adjuvant ICI treatment and are not candidates for focal therapy	Should receive standard-of-care first-line therapy
Ipilimumab combined to nivolumab in patients with sarcomatoid RCC or asymptomatic clear-cell RCC	May be considered after recurrence following adjuvant pembrolizumab
Patients with uncertain radiologic findings suggesting recurrence	Should not receive immediate systemic treatment
In asymptomatic patients with oligometastatic disease	Active surveillance may be offered

Ongoing Front-Line Trials Allow Prior ICIs

COSMIC-313 – PD(L)-1/CTLA-4 Inh monotx > 6 months

LITESPARK-012 – PD(L)-1/CTLA-4 Inh > 12 months

CARE 1 – PD(L)-1/CTLA-4 Inh > 6 months

eVOLVE-RCC02 – No Prior PD(L)-1/CTLA-4 Inh

BIOFRONT – PD(L)-1/CTLA-4 Inh > 12 months

Summary Points

- **Post-adjuvant treatment options depend on prior therapy, site and pattern of recurrence, and timing of relapse;**
- **Salvage immunotherapy has limited (if any) role in patients who progress after prior IO;**
- **For early relapses (<12 months), TKI monotherapy remains the default approach. For later relapses (>12 months), combination strategies are emerging but still evolving.**
- **Management after PD-1 failure is not yet evidence-based; current approaches are guided by expert consensus and level II data.**
- **In many real-world cases, treatment decisions hinge on access, not sequencing—offer effective therapy when available rather than reserving it for later.**

¡Gracias!

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