



Cabozantinib: present and future



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Employment: SERMAS

Honoraria for speaker engagements, advisory roles or continuous medical education: Astellas, Astra Zeneca, Janssen, MSD, Bayer, Pfizer, Eisai, Ipsen, Sanofi, Roche, BMS, Pierre Fabre, Merck

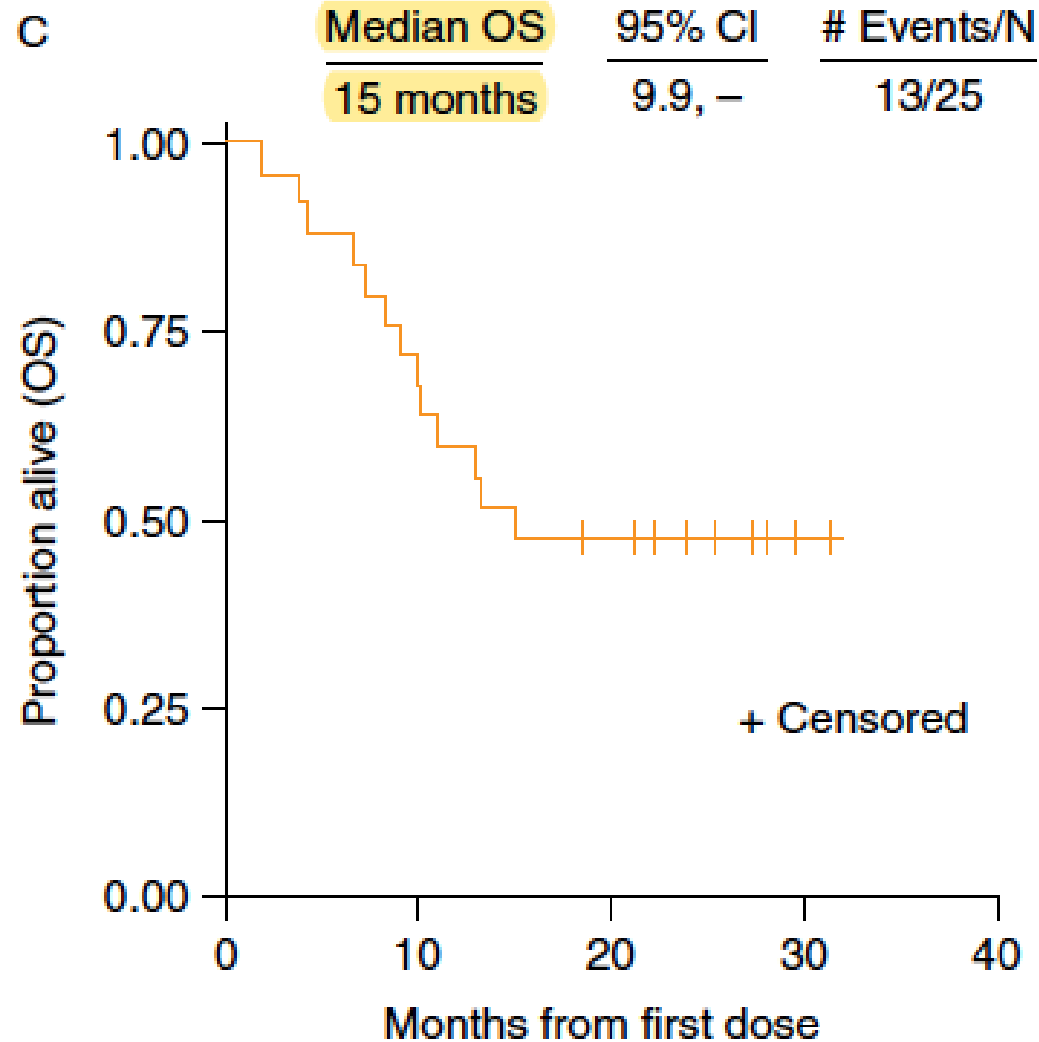
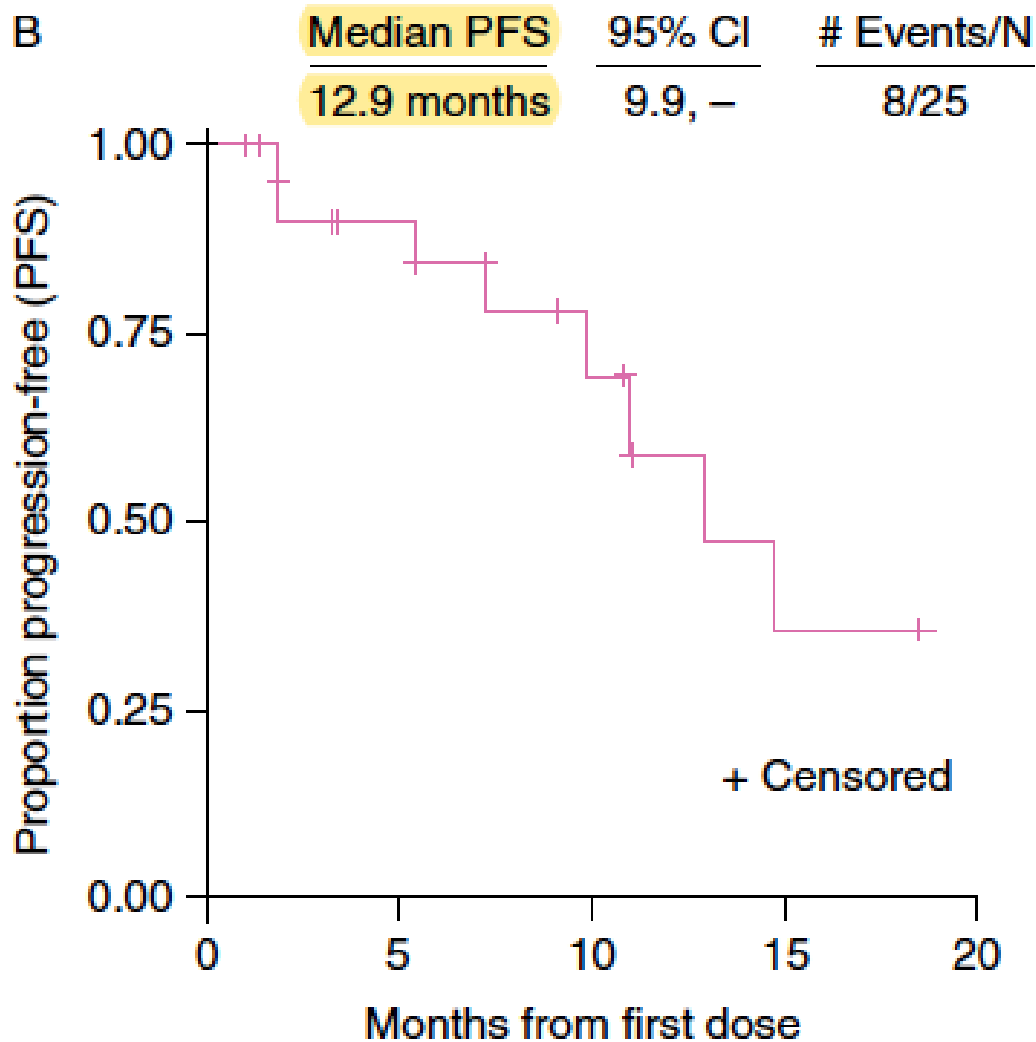
Stock Ownership: None

Research Funding: Astellas, Pfizer

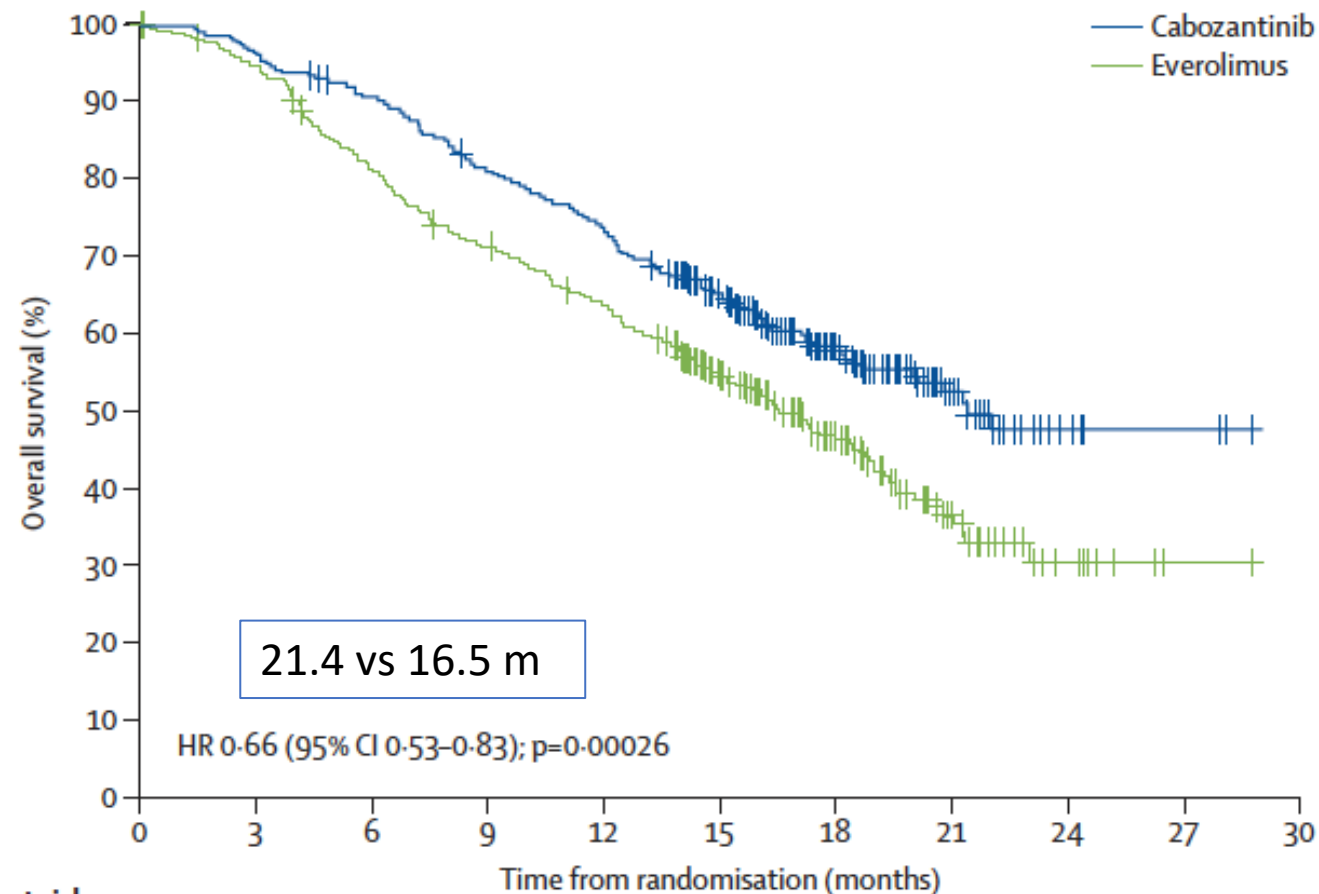
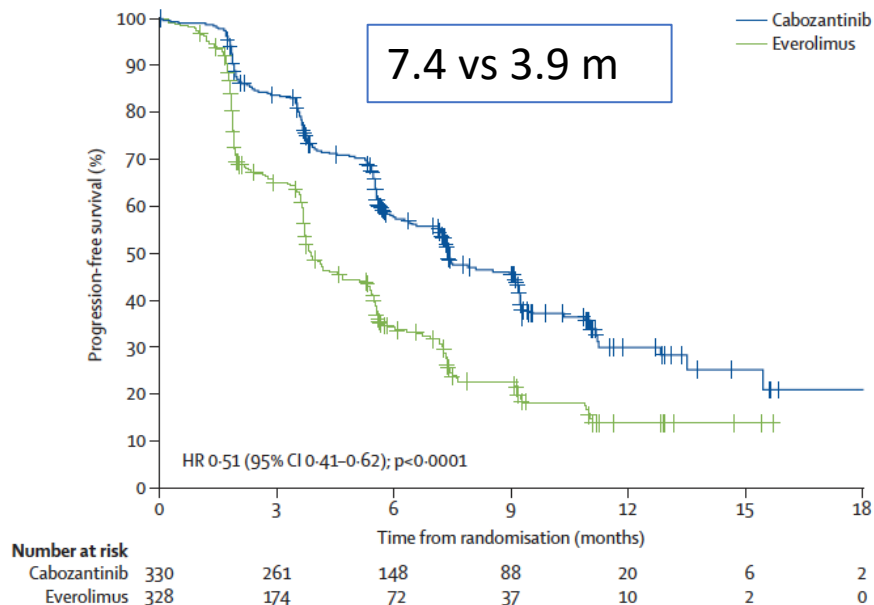
Consultant: Astellas, Roche

- **Classic role of Cabozantinib (2L and further lines of therapy)**
- **Role of cabozantinib in 1L**
- **Role of cabozantinib in non-clear cell renal cancer**
- **Future of cabozantinib**
- **Final remarks**

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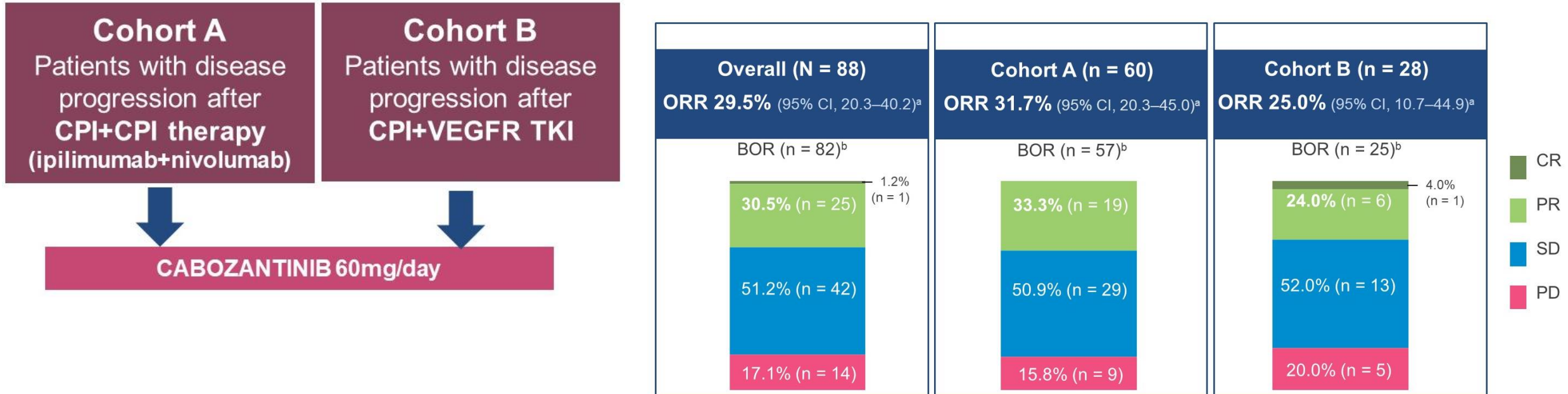
Cabozantinib *versus* Everolimus: METEOR study



	Cabozantinib N=330		Everolimus N=328	
	IRC	Investigator	IRC	Investigator
Objective response rate (95% CI)	17 (13-22)	24 (19-29)	3 (2-6)	4 (2-7)
Best overall response, n (%)				
Confirmed complete response	0	0	0	0
Confirmed partial response	57 (17)	78 (24)	11 (3)	14 (4)
Stable disease	216 (65)	209 (63)	203 (62)	205 (63)
Progressive disease	41 (12)	29 (9)	88 (27)	87 (27)
Not evaluable or missing	16 (5)	14 (4)	26 (8)	22 (7)

STUDY DESIGN AND PATIENTS

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



- Classic role of Cabozantinib (2L and further lines of therapy)
- **Role of cabozantinib in 1L**
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Key inclusion criteria^{1,2}

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

N = 651

R
1:1

NIVO 240 mg IV Q2W
+ CABO 40 mg PO QD

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

*Treat until RECIST v1.1-
defined progression or
unacceptable toxicity^b*

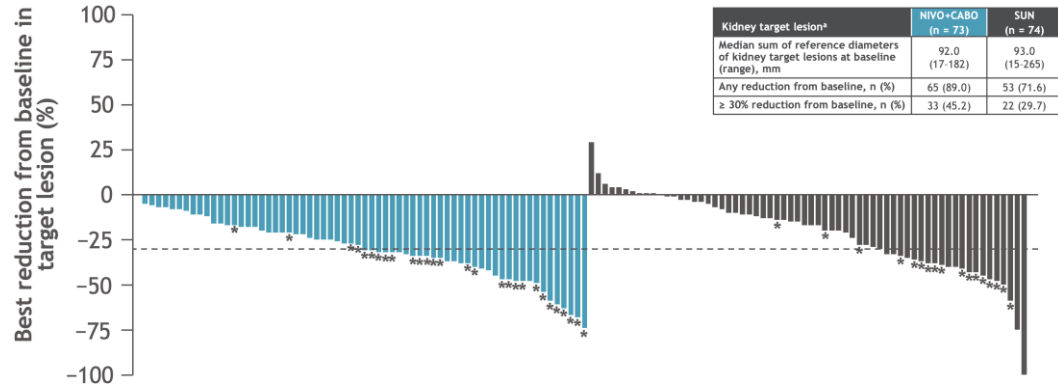
Stratification factors:

- IMDC risk score (favorable vs. intermediate vs. poor risk)
- Tumor PD-L1 expression ($\geq 1\%$ vs. $< 1\%$ or indeterminate)^a
- Geographic region (US/Canada/W. Europe/N. Europe vs. rest of the world)

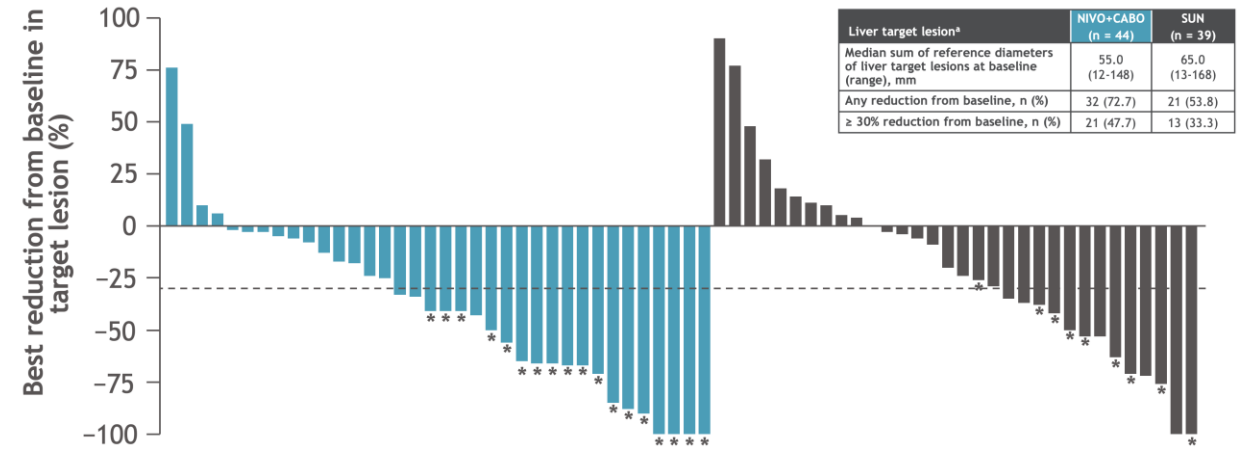
Variable ^a	NIVO+CABO (n = 323)	SUN (n = 328)
Confirmed ORR (95% CI), %	55.7 (50.1–61.2)	28.4 (23.5–33.6)
Confirmed BOR, n (%)		
Complete response	40 (12.4)	17 (5.2)
Partial response	140 (43.3)	76 (23.2)
Stable disease	105 (32.5)	134 (40.9)
Progressive disease	20 (6.2)	45 (13.7)
Unable to determine	18 (5.6)	55 (16.8)
Not reported	0	1 (0.3)
Median TTR (range), months	2.8 (1.0–22.3)	4.2 (1.7–30.4)
Median DOR (95% CI), months	23.1 (20.2–27.9)	15.1 (9.9–20.5)

^aResponse was assessed according to RECIST v1.1, per BICR.
BOR, best overall response; DOR, duration of response; TTR, time to response.

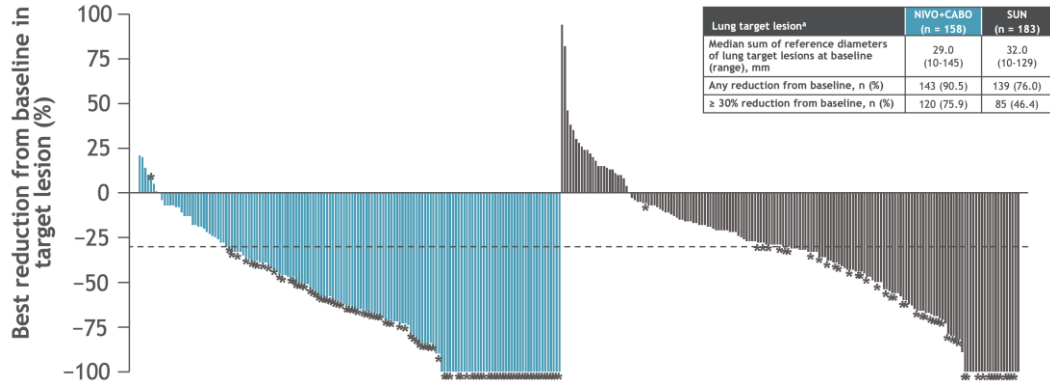
A. Kidney



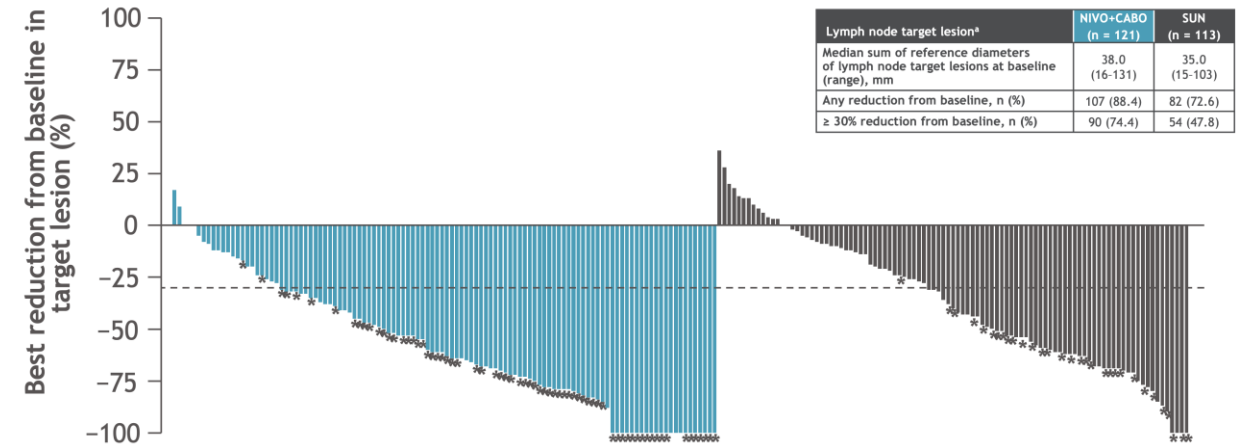
B. Liver



C. Lung



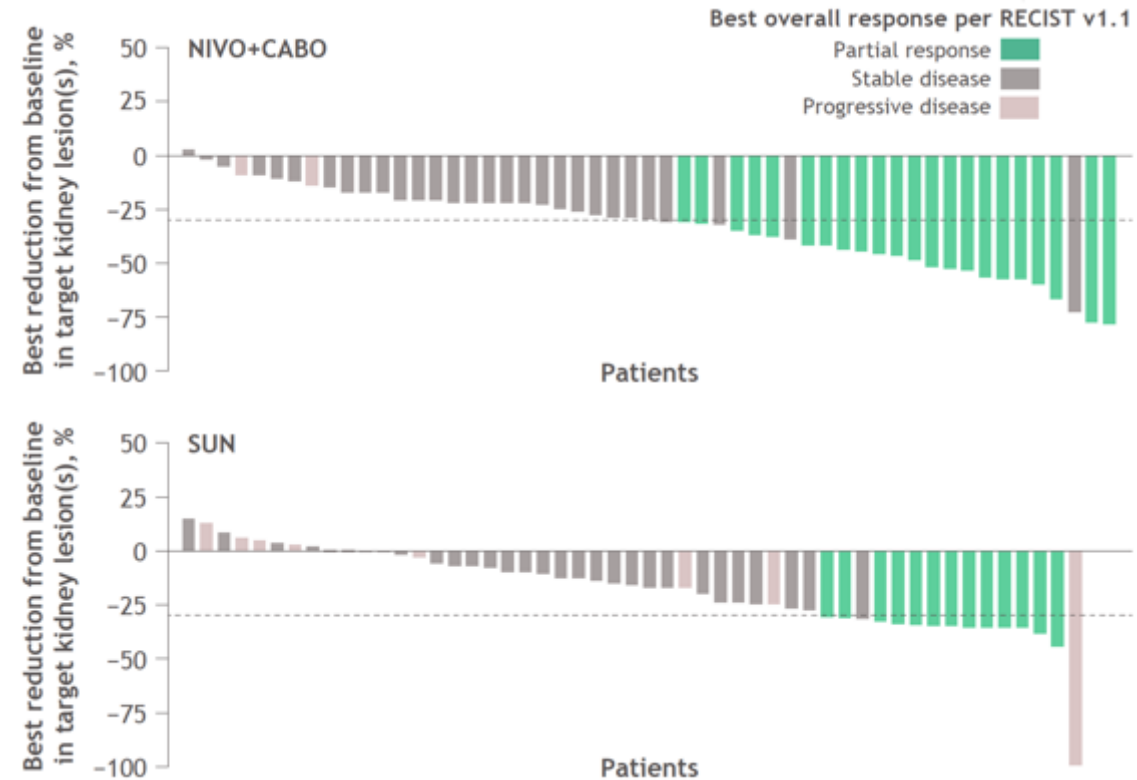
D. Lymph node



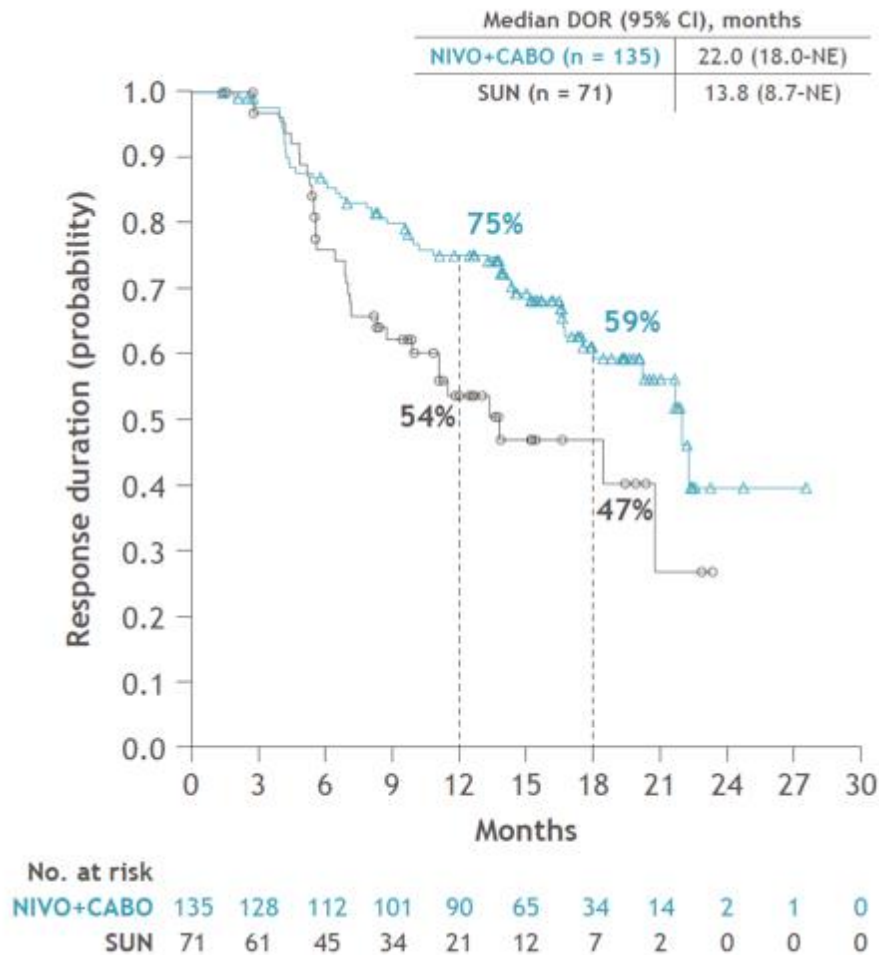
Best overall response per BICR in subgroups by prior nephrectomy status

Outcome	With prior nephrectomy		Without prior nephrectomy	
	NIVO+CABO (n=222)	SUN (n=233)	NIVO+CABO (n=101)	SUN (n=95)
Confirmed ORR, % (95% CI)	60.8 (54.1–67.3)	30.5 (24.6–36.8)	41.6 (31.9–51.8)	23.2 (15.1–32.9)
Best overall response, n (%)				
Complete response	25 (11.3)	14 (6.0)	5 (5.0)	0
Partial response	110 (49.5)	57 (24.5)	37 (36.6)	22 (23.2)
Stable disease	67 (30.2)	93 (39.9)	41 (40/6)	43 (45.3)
Progressive disease	13 (5.9)	31 (13.3)	7 (6.9)	14 (14.7)
Unable to determine	7 (3.2)	38 (16.3)	11 (10.9)	15 (15.8)
Not reported	0	0	0	1 (1.1)
Median (Q1–Q3) time to response, months	2.8 (2.8–3.3)	4.1 (2.8–7.1)	2.8 (2.8–5.4)	5.5 (4.0–8.3)

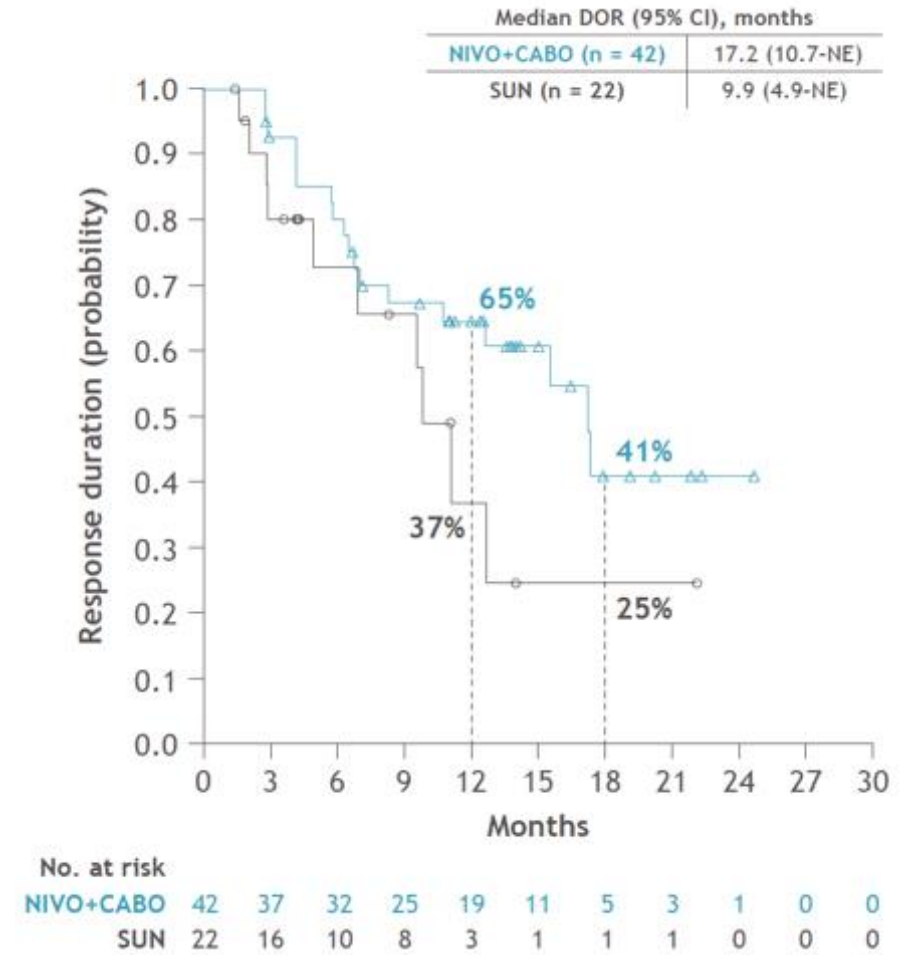
Maximum reduction from baseline in target kidney lesion(s) in all response evaluable pts without prior nephrectomy



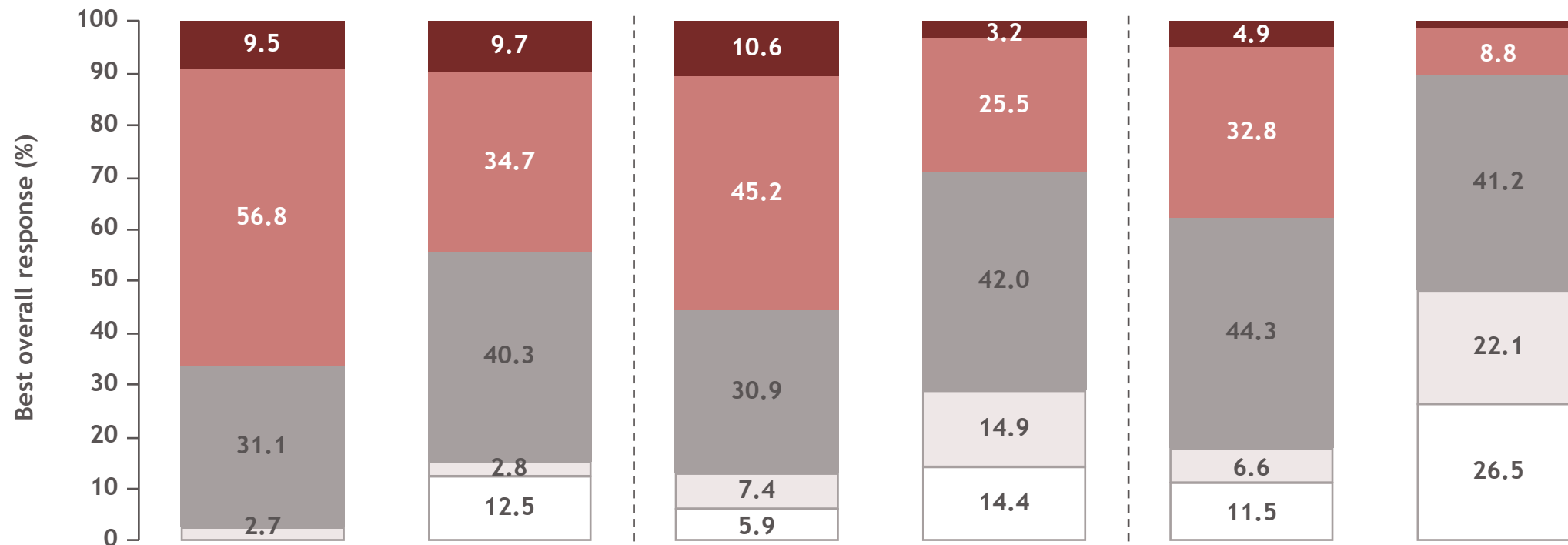
DOR per BICR with prior nephrectomy



DOR per BICR without prior nephrectomy



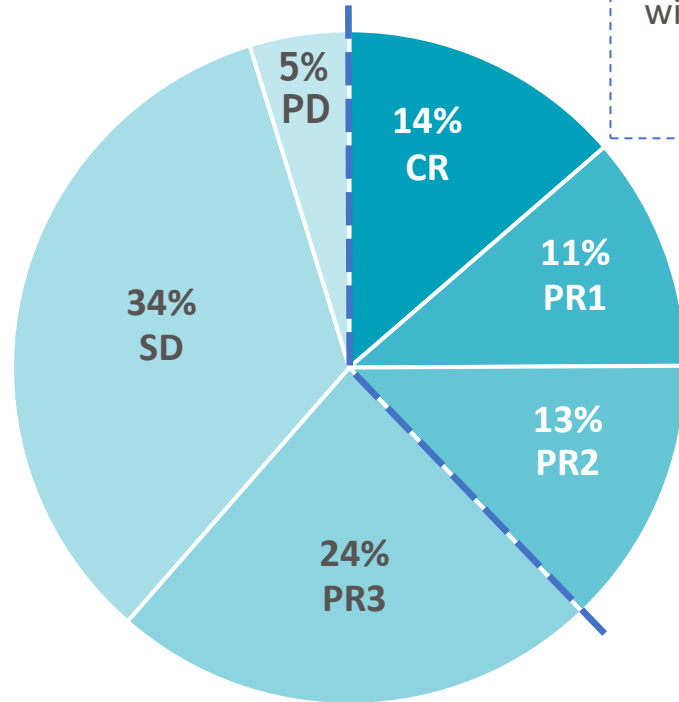
■ Complete response
 ■ Partial response
 ■ Stable disease
 ■ Progressive disease
 ■ Unable to determine



	Favorable risk ^a		Intermediate risk ^b		Poor risk ^c	
	NIVO+CABO (n = 74)	SUN (n = 72)	NIVO+CABO (n = 188)	SUN (n = 188)	NIVO+CABO (n = 61)	SUN (n = 68)
ORR (95% CI), %	66.2 (54.3-76.8)	44.4 (32.7-56.6)	55.9 (48.4-63.1)	28.7 (22.4-35.8)	37.7 (25.6-51.0)	10.3 (4.2-20.1)
mTTR (range), mo ^d	2.8 (1.5-9.7)	4.1 (1.7-20.2)	2.8 (1.0-8.3)	4.9 (1.7-13.8)	2.9 (2.4-11.0)	3.1 (2.8-12.4)
mDOR (95% CI), mo ^d	NR (21.7-NE)	13.3 (9.9-NE)	20.2 (16.5-NE)	12.7 (7.0-NE)	NR (15.5-NE)	4.9 (2.8-13.8)

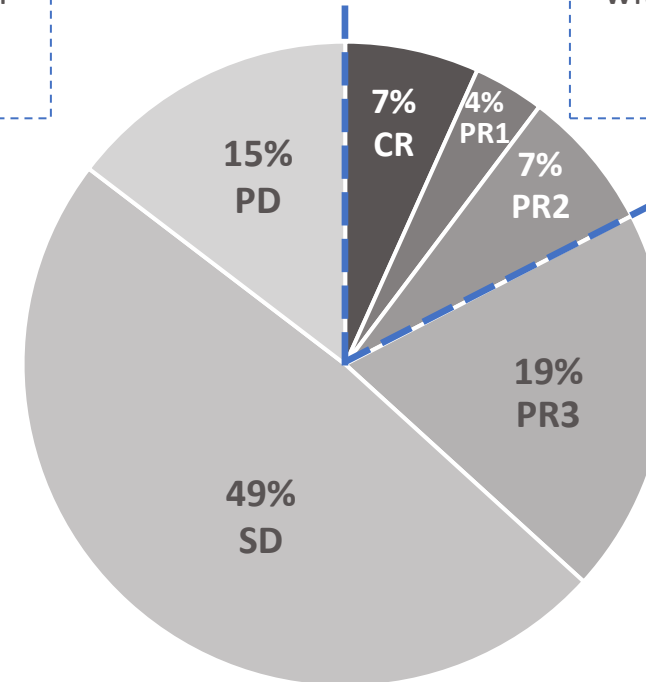
Distribution of DepOR subgroups by treatment arm

NIVO+CABO
N = 293



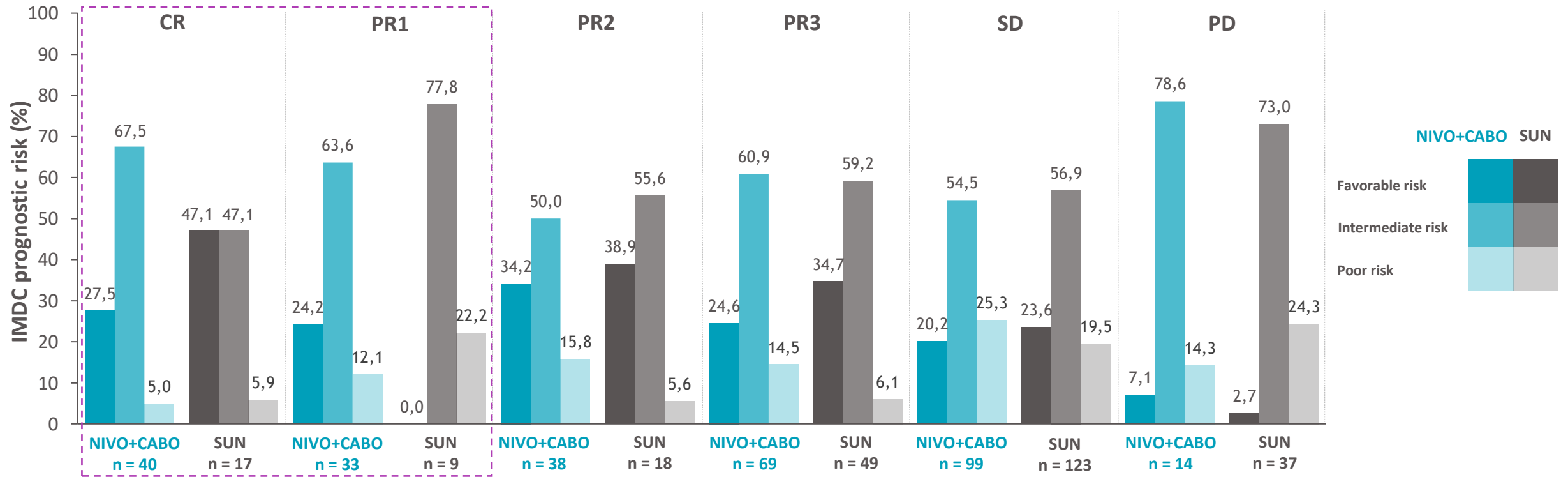
Patients alive at 6 months with $\geq 60\%$ best reduction in target lesions^b: **38%^c**

SUN
N = 253



Patients alive at 6 months with $\geq 60\%$ best reduction in target lesions^b: **17%^c**

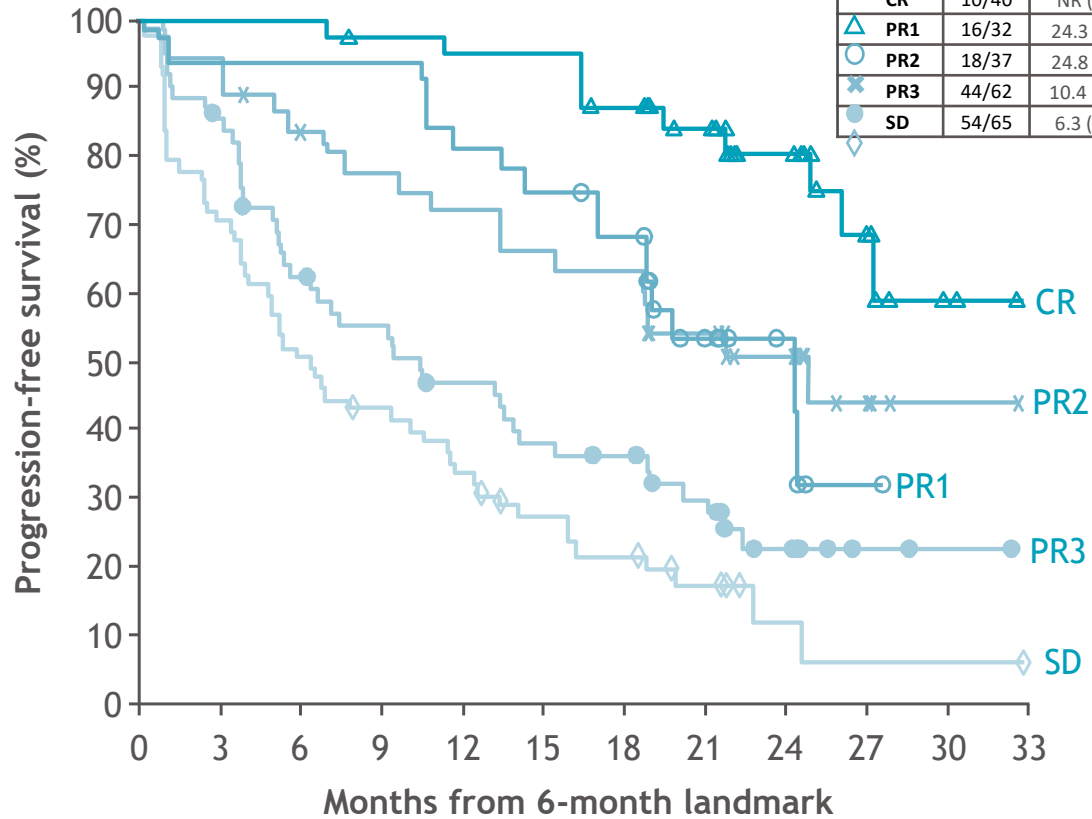
- Among patients alive at the 6-month landmark, greater proportions receiving NIVO+CABO had CR, PR1, or PR2 versus SUN
- A lower proportion of patients receiving NIVO+CABO had PD versus SUN



- IMDC prognostic risk group was generally similar between treatment arms within subgroups, with the exception of CR and PR1

NIVO+CABO

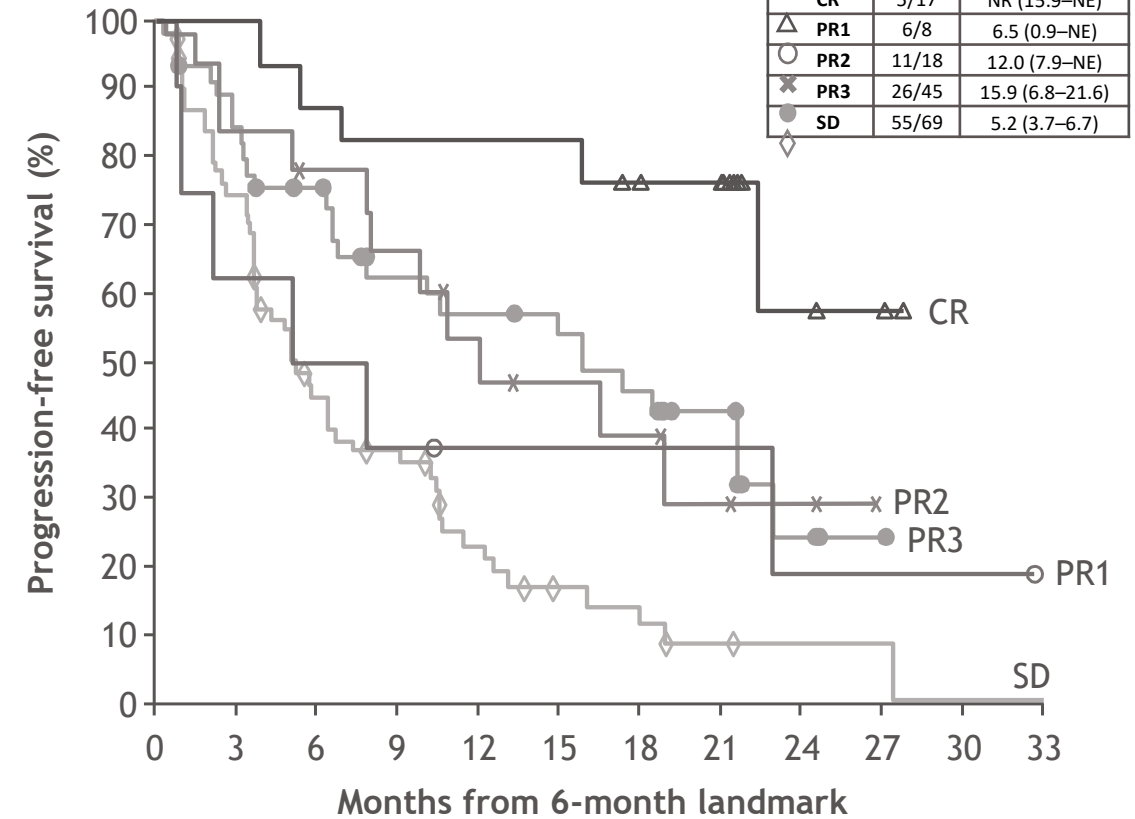
DepOR subgroup	Events, n/N	Median PFS (95% CI), months
CR	10/40	NR (26.0–NE)
△ PR1	16/32	24.3 (17.0–NE)
○ PR2	18/37	24.8 (13.4–NE)
× PR3	44/62	10.4 (5.5–14.0)
● SD	54/65	6.3 (4.0–10.6)



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33
CR	40	40	40	38	37	37	33	28	20	9	2	0
PR1	32	30	30	30	26	24	21	10	5	1	0	0
PR2	37	34	29	27	25	23	22	17	12	5	1	0
PR3	62	52	37	32	26	21	19	14	7	2	1	0
SD	65	46	33	27	21	15	12	7	2	1	1	0

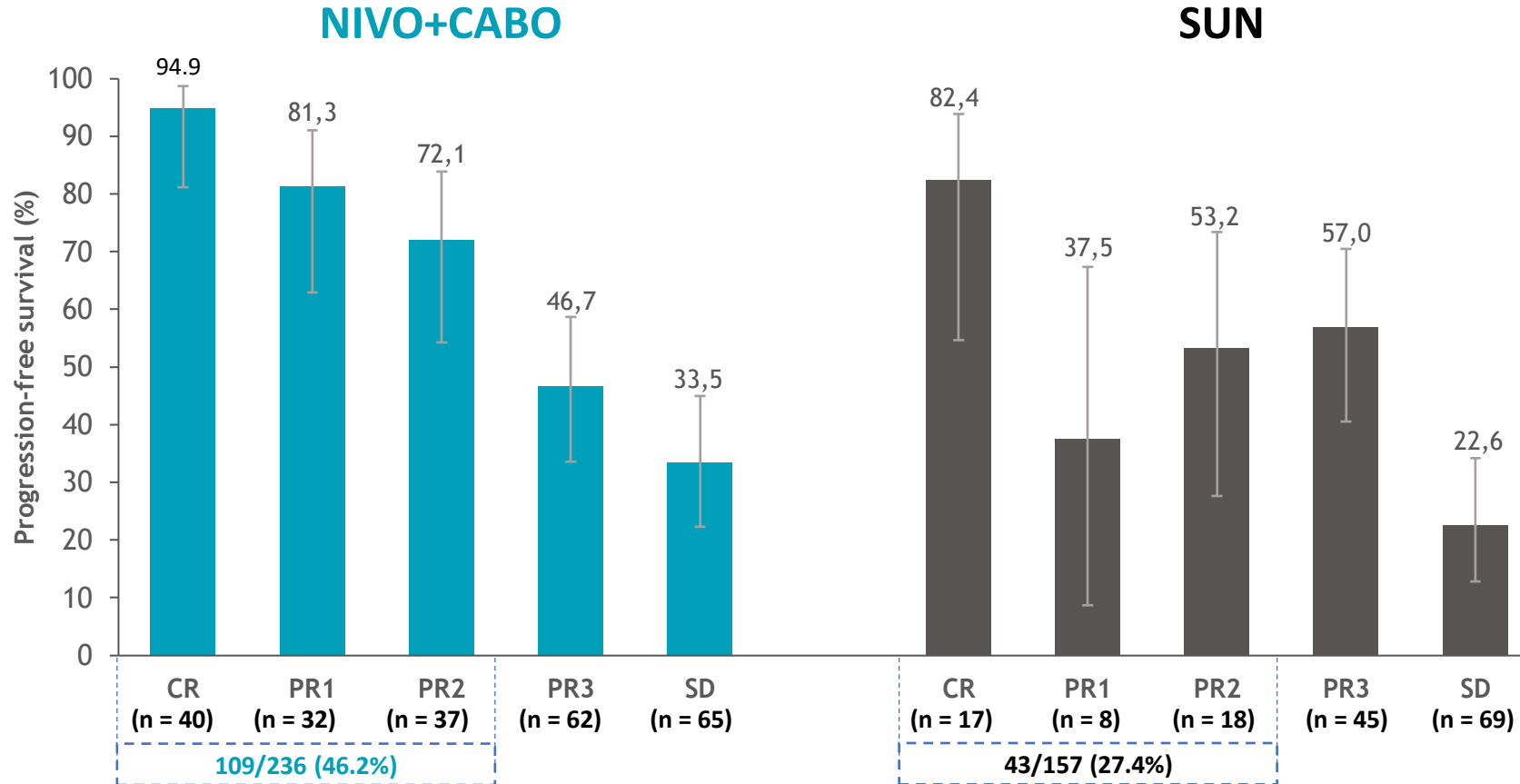
SUN

DepOR subgroup	Events, n/N	Median PFS (95% CI), months
CR	5/17	NR (15.9–NE)
△ PR1	6/8	6.5 (0.9–NE)
○ PR2	11/18	12.0 (7.9–NE)
× PR3	26/45	15.9 (6.8–21.6)
● SD	55/69	5.2 (3.7–6.7)

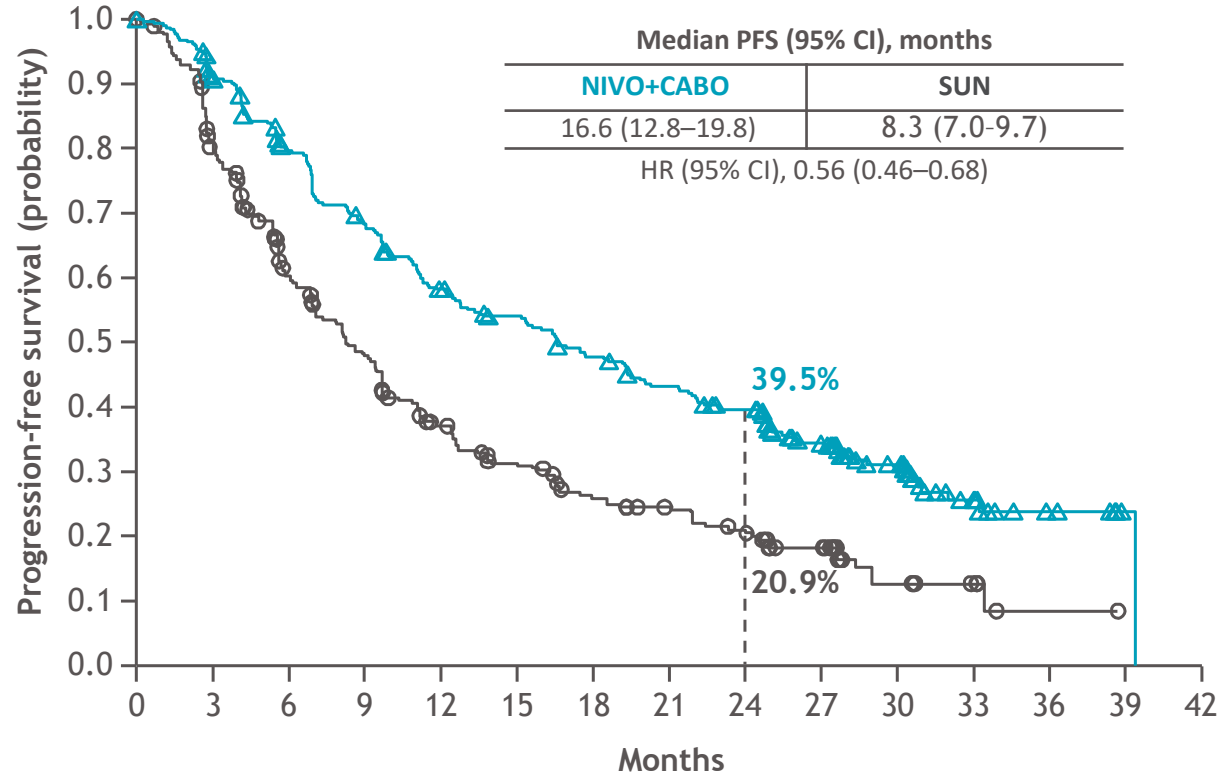


No. at risk	0	3	6	9	12	15	18	21	24	27	30	33
CR	17	17	15	14	14	14	12	11	3	2	0	0
PR1	8	5	4	3	2	2	2	2	1	1	1	0
PR2	18	15	13	11	8	6	5	3	2	0	0	0
PR3	45	37	31	23	21	19	16	10	3	1	0	0
SD	69	49	27	20	11	6	5	2	1	1	0	0

12-month PFS rates by DepOR subgroups



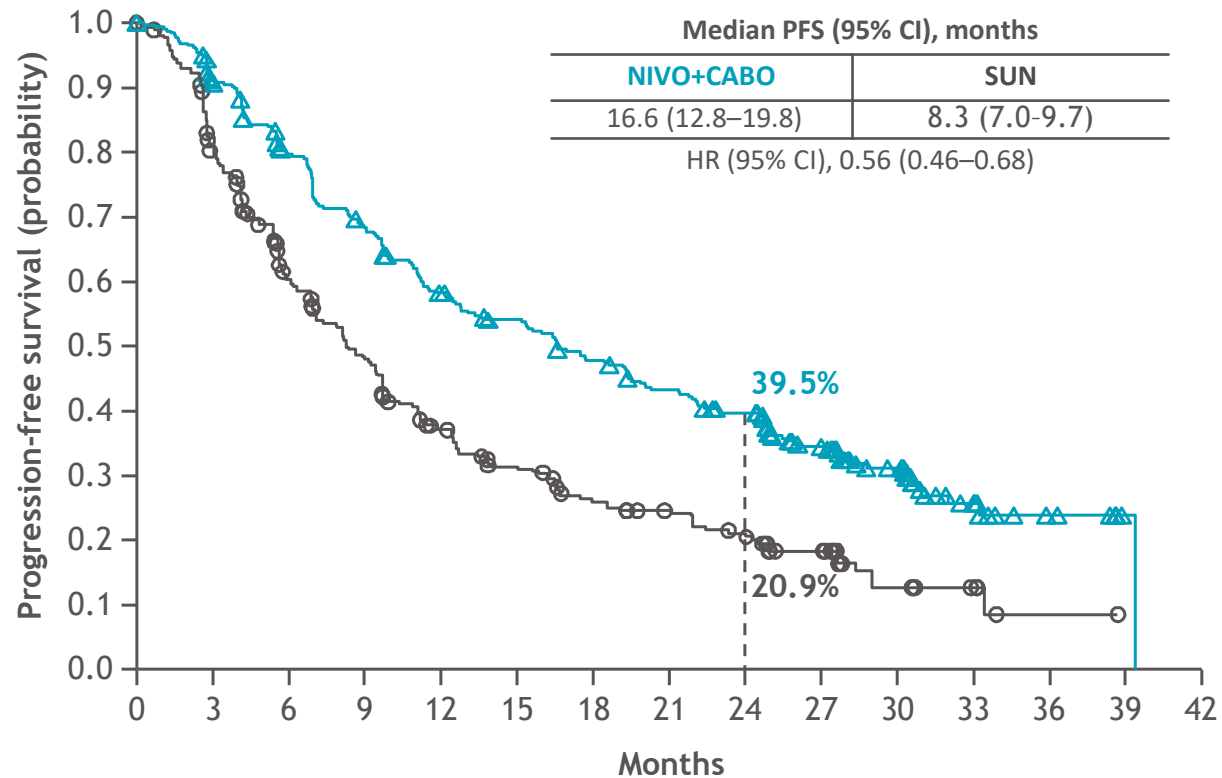
Recently update CM9ER: PFS



No. at risk

NIVO+CABO	323	281	238	203	170	155	136	121	108	77	47	19	6	1	0
SUN	328	233	161	125	91	72	57	48	41	28	10	5	1	0	0

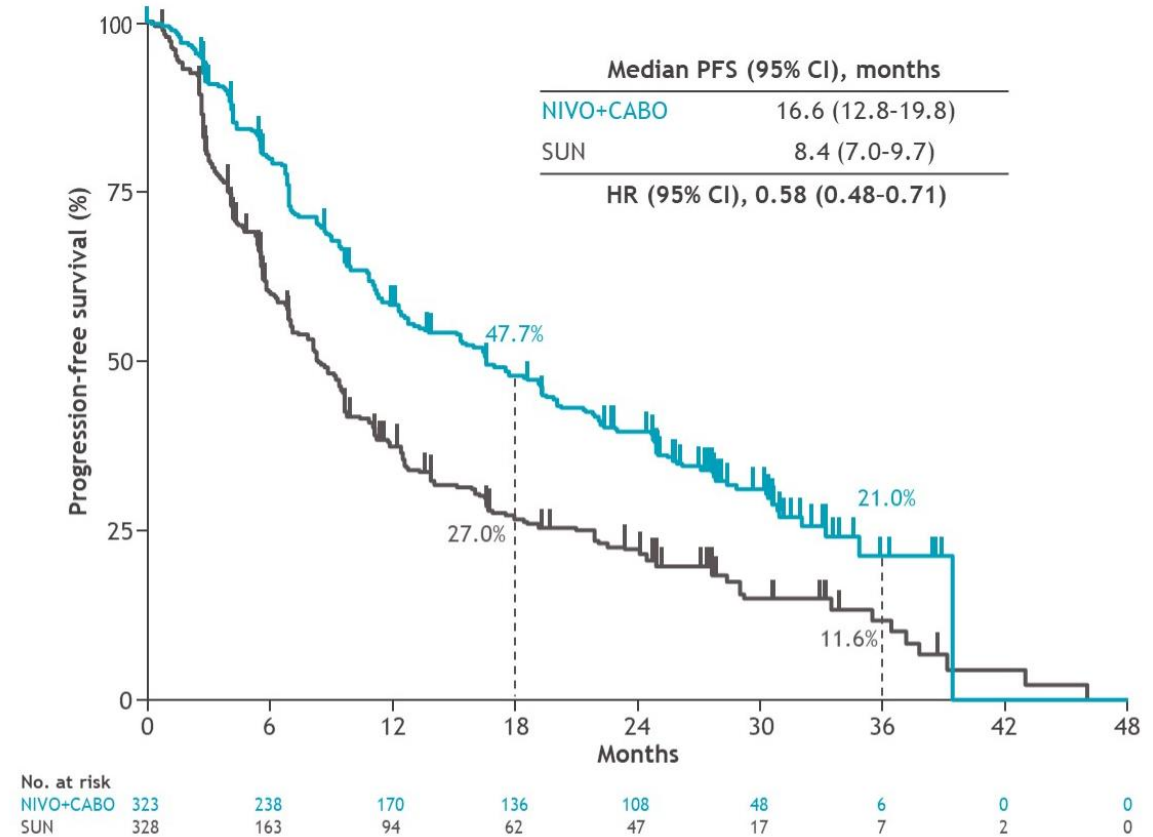
Recently update CM9ER: PFS

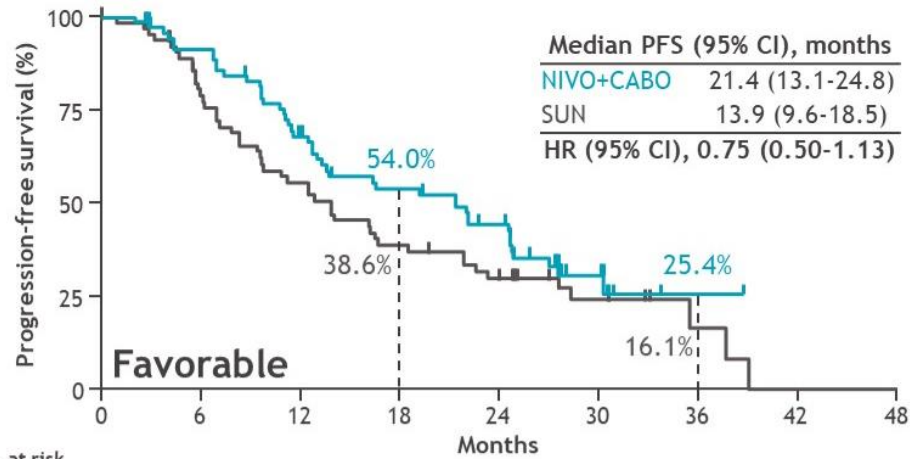


No. at risk

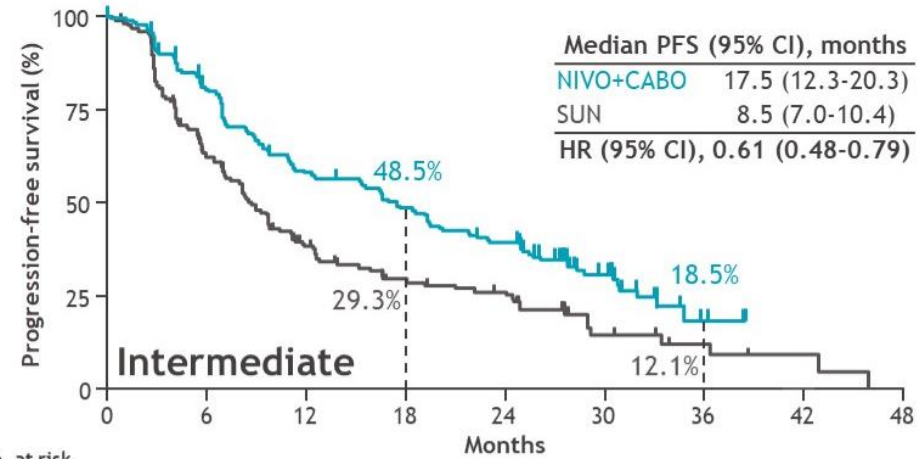
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	
NIVO+CABO	323	281	238	203	170	155	136	121	108	77	47	19	6	1	0
SUN	328	233	161	125	91	72	57	48	41	28	10	5	1	0	0

FU: 44 months

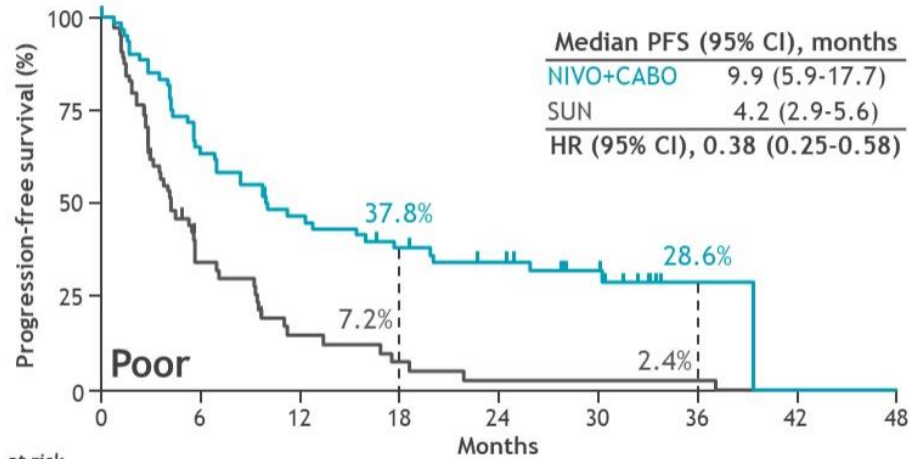




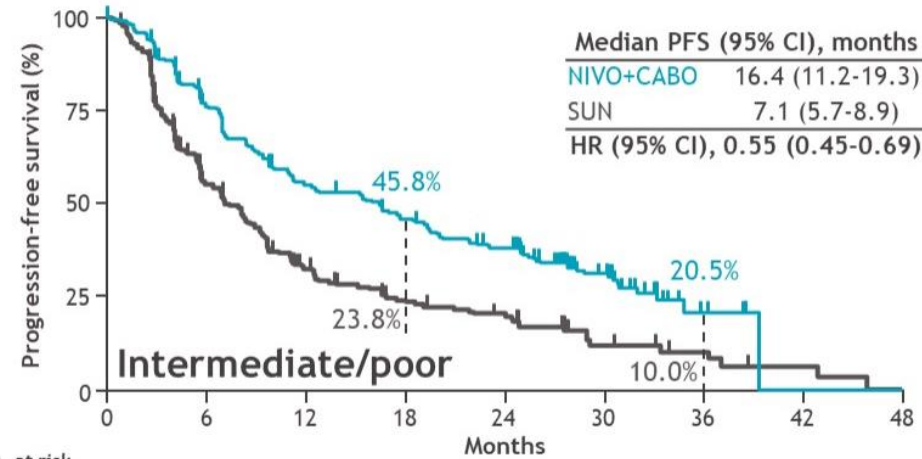
No. at risk	0	6	12	18	24	30	36	42	48
NIVO+CABO	74	63	45	34	26	8	1	0	0
SUN	72	47	33	23	17	8	2	0	0



No. at risk	0	6	12	18	24	30	36	42	48
NIVO+CABO	188	137	98	81	65	29	4	0	0
SUN	188	100	55	36	29	8	4	2	0



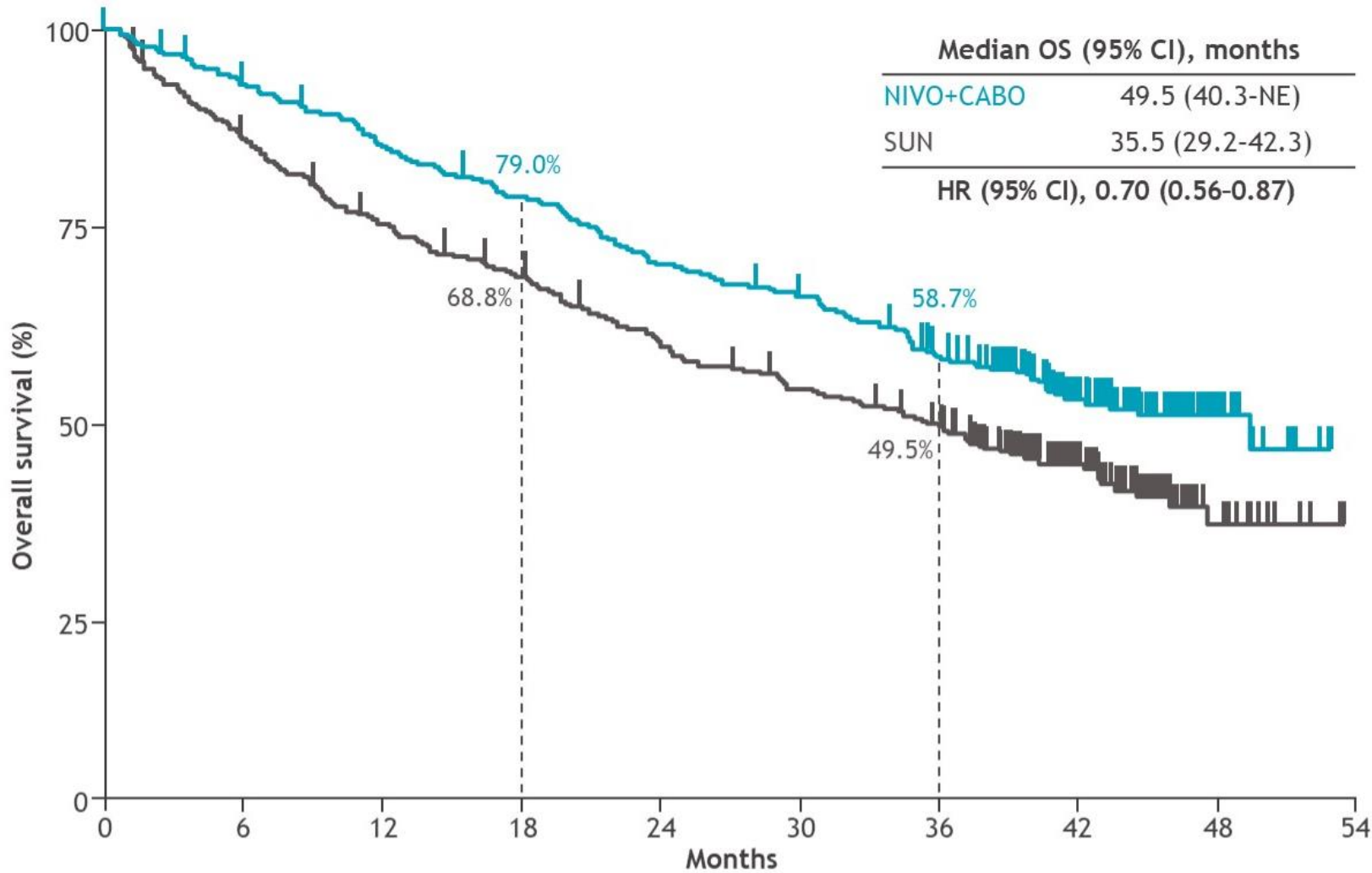
No. at risk	0	6	12	18	24	30	36	42	48
NIVO+CABO	61	38	27	21	17	11	1	0	0
SUN	68	16	6	3	1	1	1	0	0



No. at risk	0	6	12	18	24	30	36	42	48
NIVO+CABO	249	175	125	102	82	40	5	0	0
SUN	256	116	61	39	30	9	5	2	0

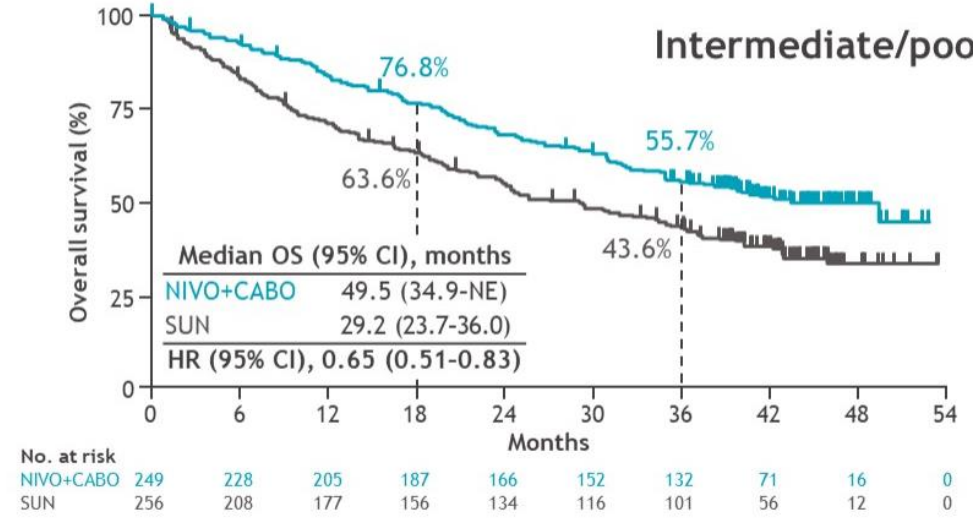
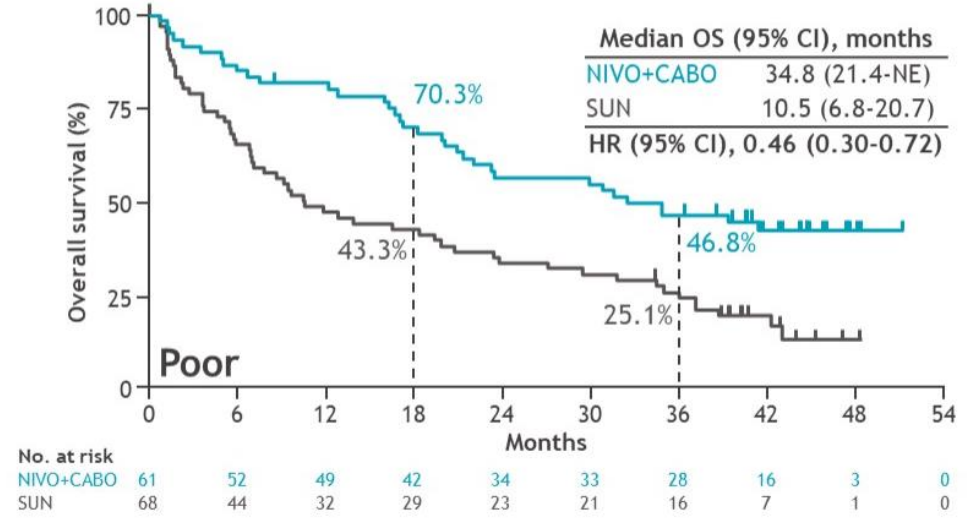
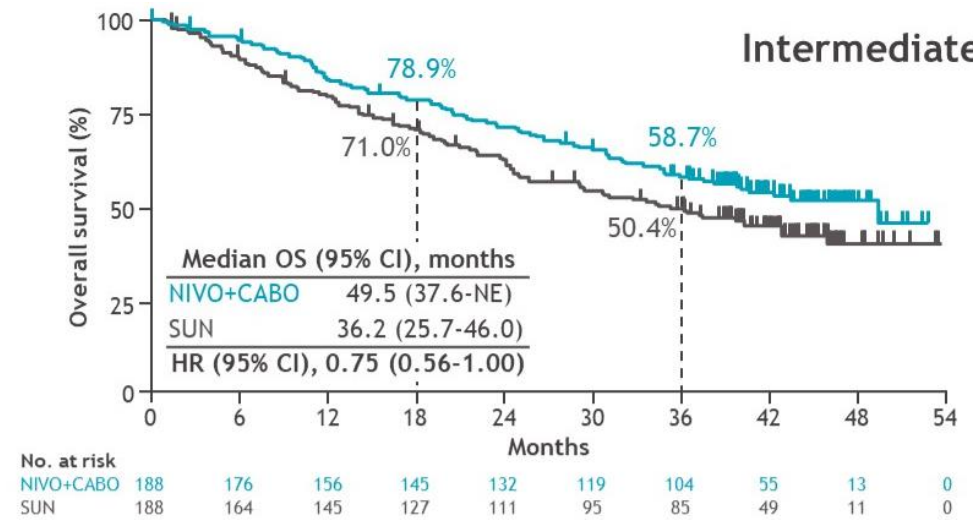
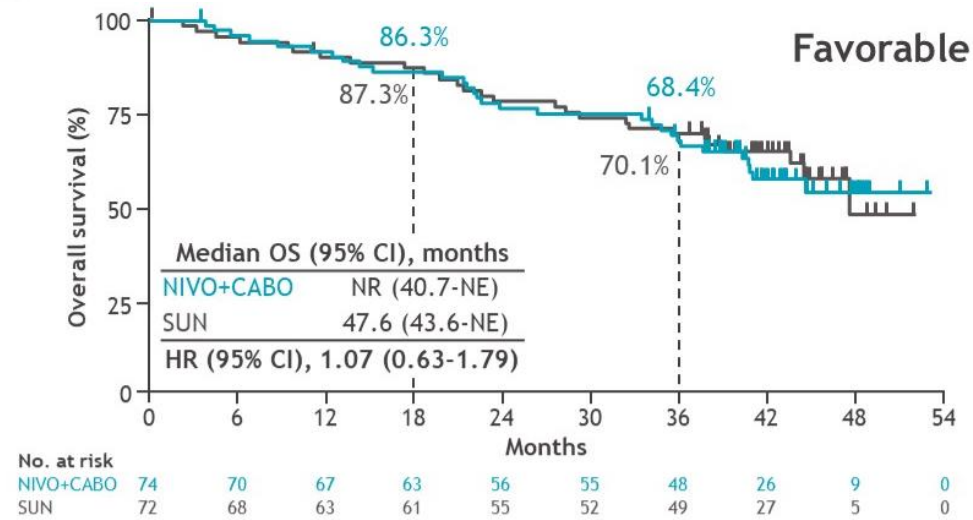
Median follow-up for OS, 44.0 months. Unstratified Cox proportional hazard model used for HR.

CM9ER: Overall survival in the ITT population (FU: 44 m)



No. at risk	0	6	12	18	24	30	36	42	48	54
NIVO+CABO	323	298	272	250	222	207	180	97	25	0
SUN	328	276	240	217	189	168	150	83	17	0

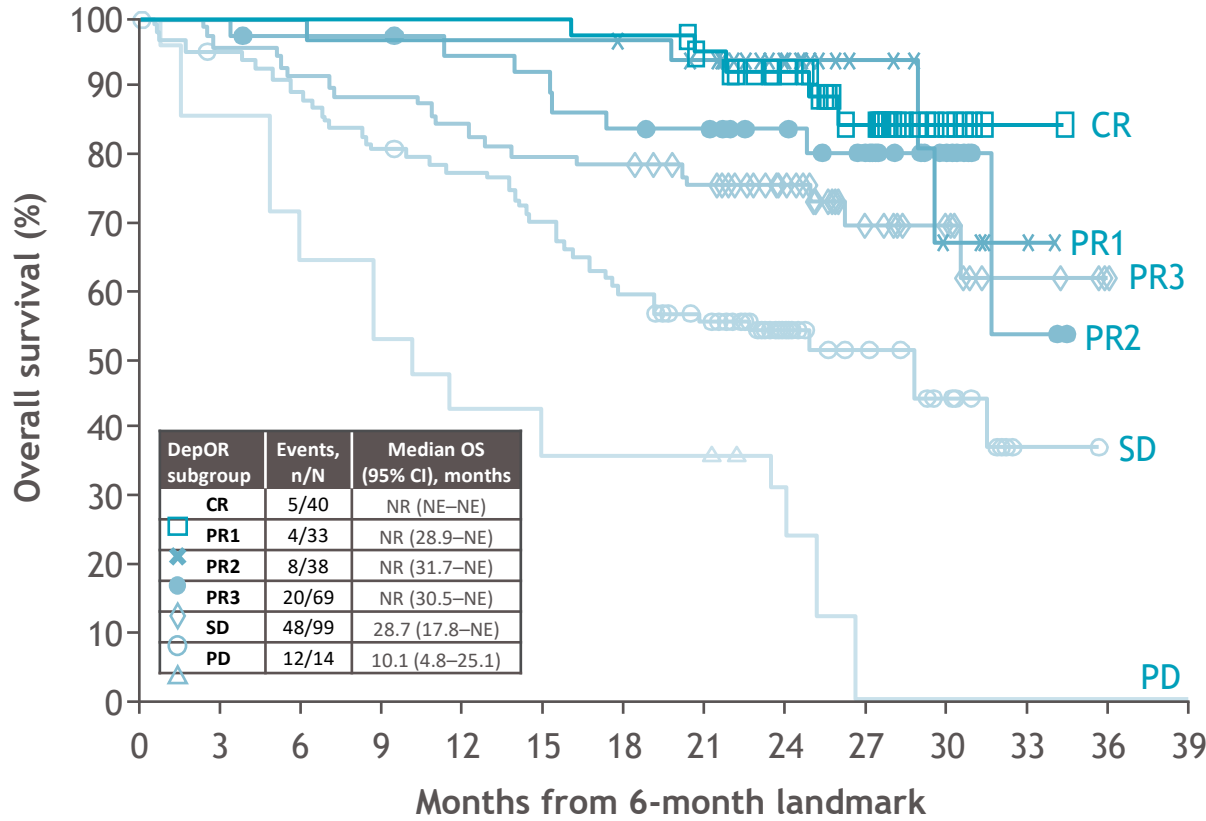
CM9ER: Overall survival by IMDC subgroup (FU: 44 m)



Median follow-up for OS, 44.0 months. Unstratified Cox proportional hazard model used for HR.

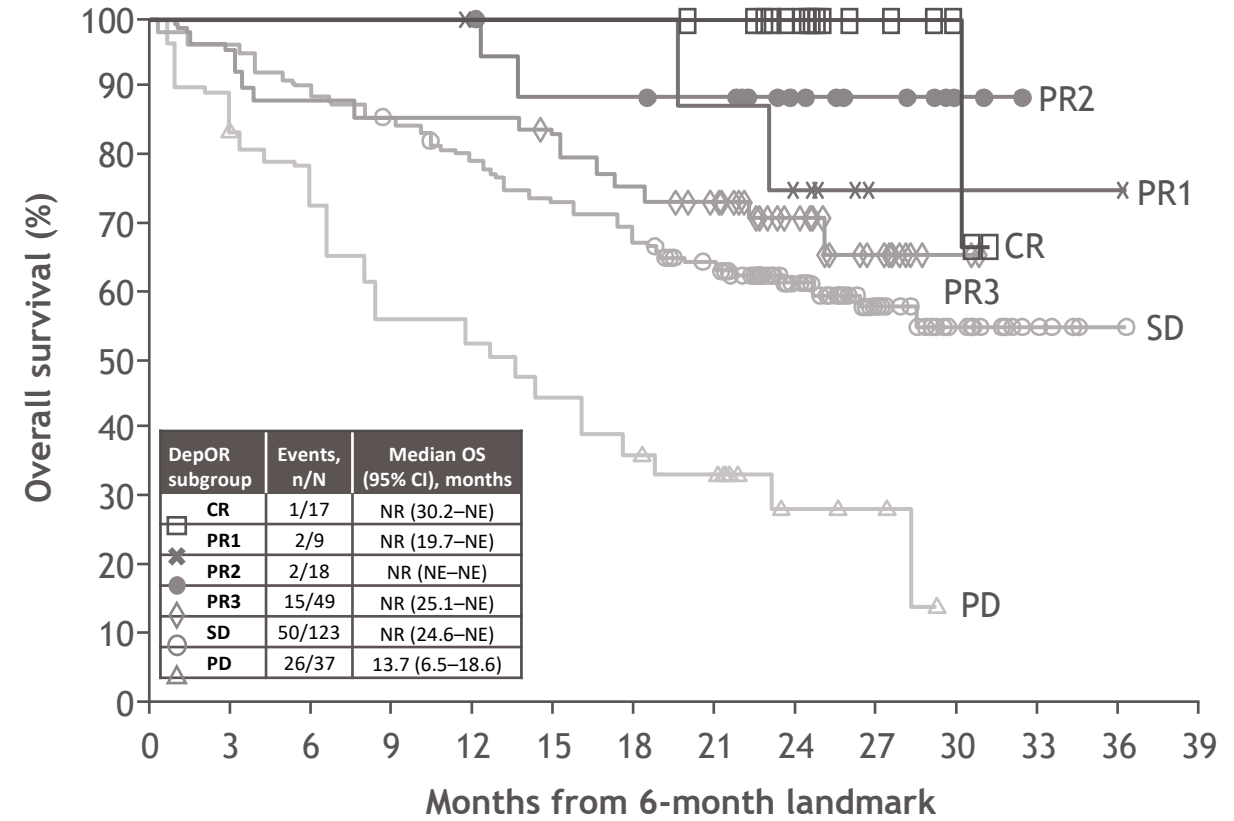
OS by DepOR subgroups (6-month landmark analysis)

NIVO+CABO



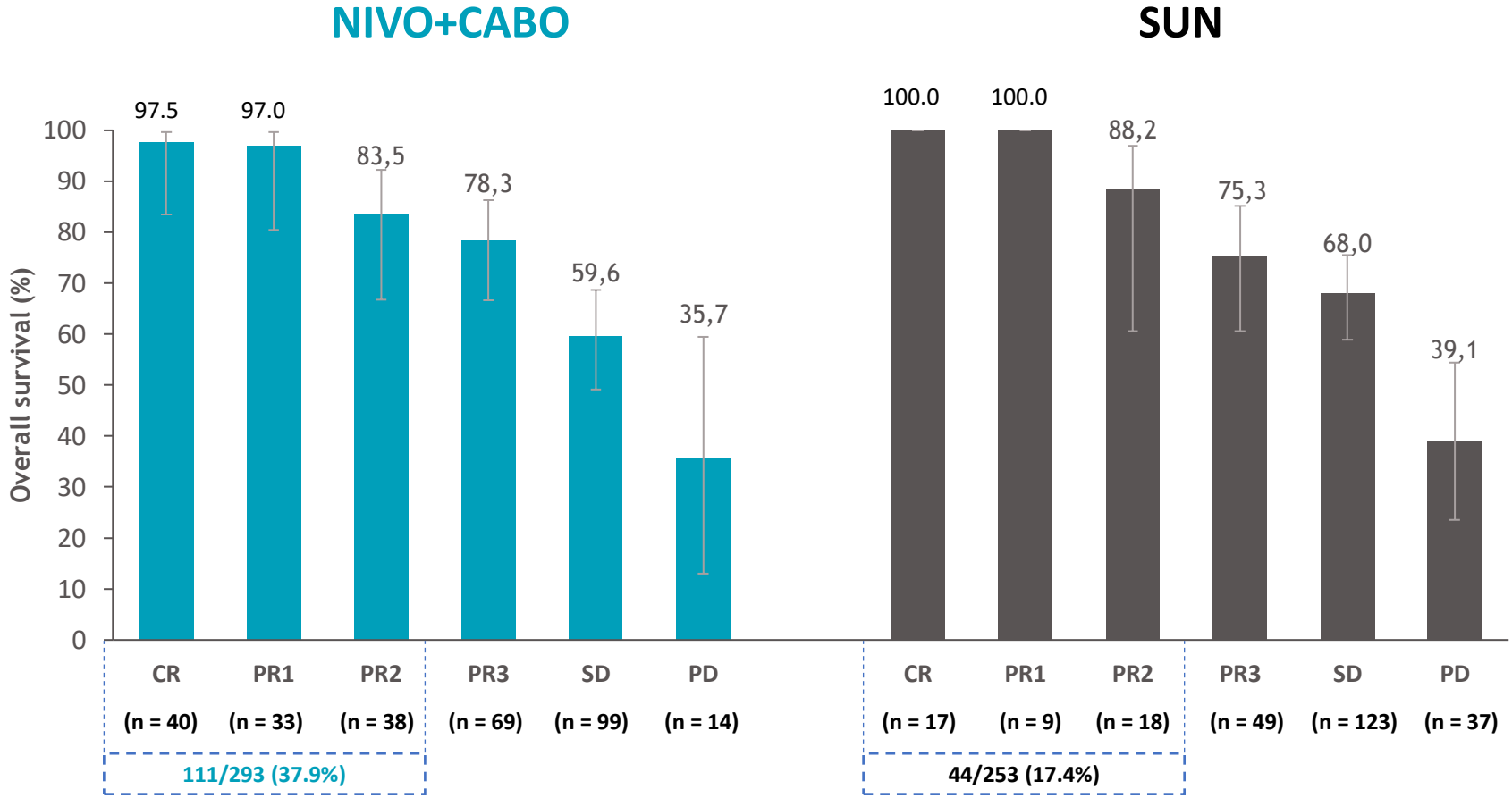
No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39
CR	40	40	40	40	40	40	39	36	29	18	8	1	0	0
PR1	33	33	33	32	32	32	31	29	19	10	4	2	0	0
PR2	38	38	36	36	34	33	30	29	25	18	9	2	0	0
PR3	69	66	63	61	58	55	54	49	36	17	11	4	1	0
SD	99	92	86	78	74	67	57	49	25	16	9	1	0	0
PD	14	12	9	8	6	5	5	5	2	0	0	0	0	0

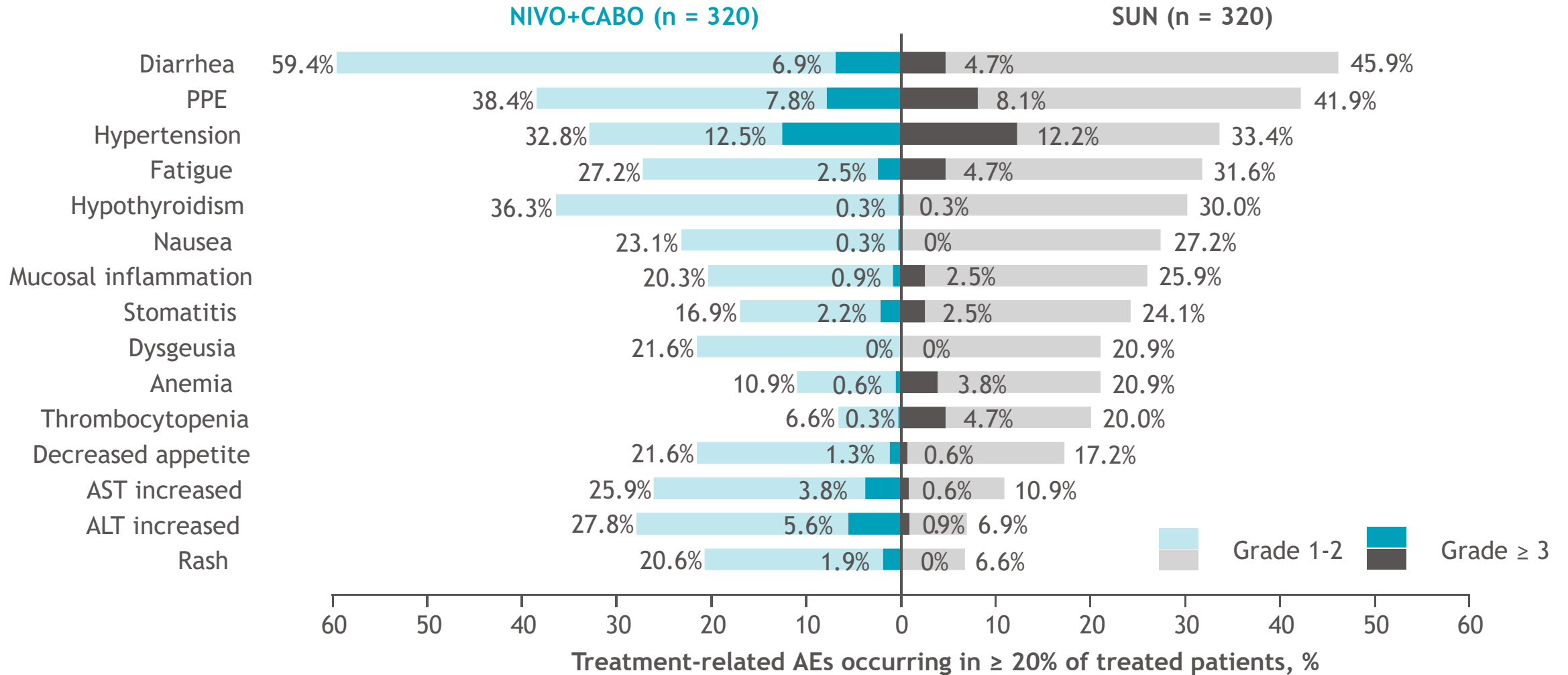
SUN



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39
CR	17	17	17	17	17	17	17	17	16	11	6	3	0	0
PR1	9	9	9	9	8	8	8	7	5	1	1	1	1	0
PR2	18	18	18	18	18	15	15	14	9	6	2	0	0	0
PR3	49	46	43	42	42	39	36	32	18	9	2	0	0	0
SD	123	118	110	104	96	88	82	72	51	27	13	5	1	0
PD	37	31	26	20	18	16	14	11	4	3	0	0	0	0

18-month OS rates by DepOR subgroups



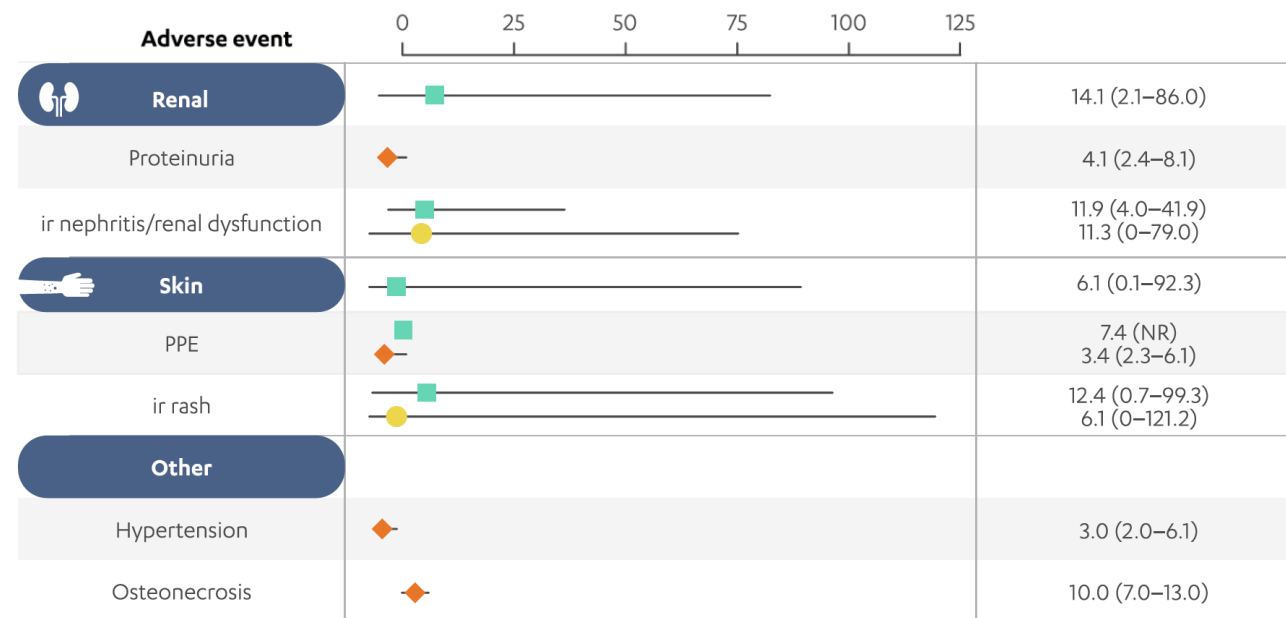


Management of AEs with Cabo-Nivo

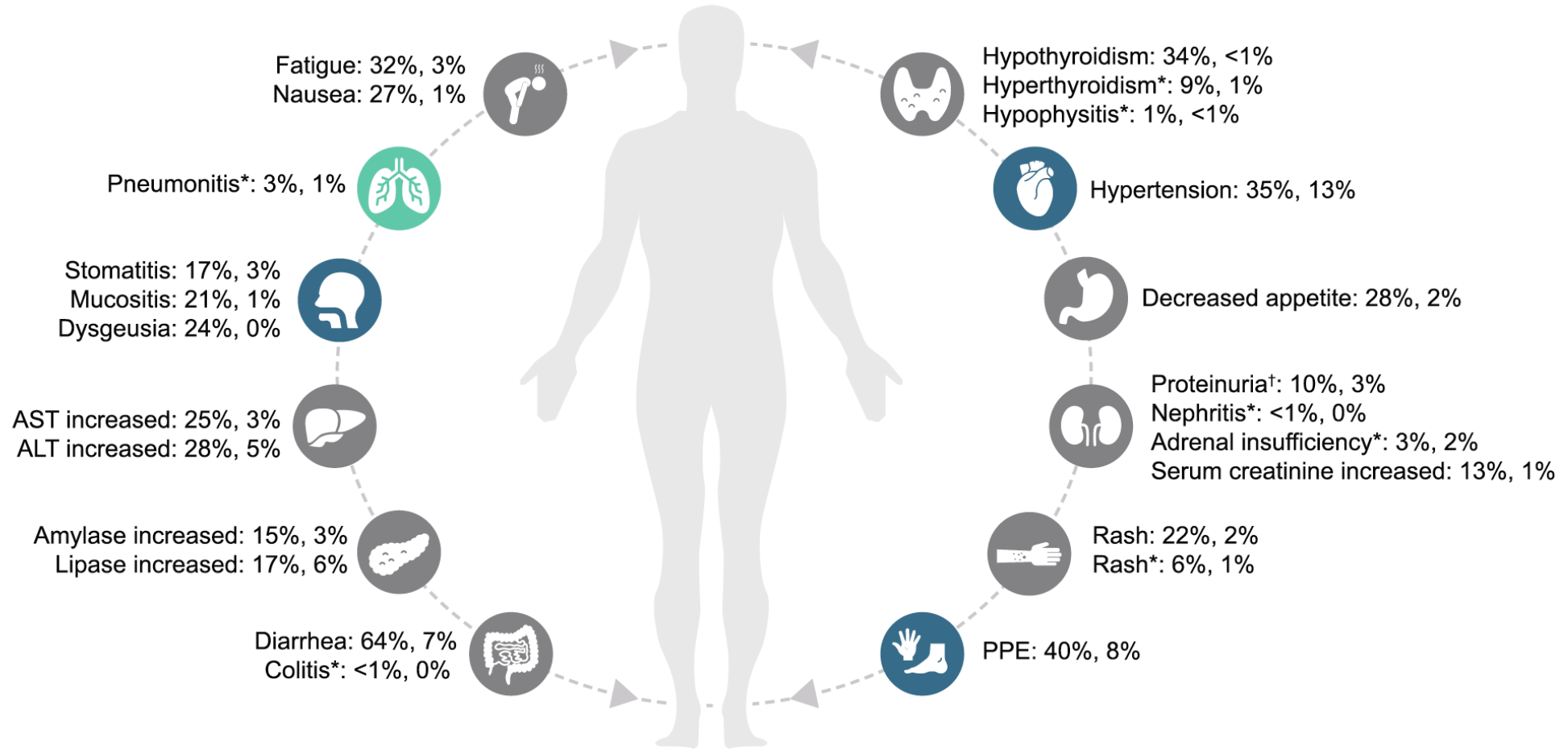
Median time-to-onset (range/IQR), weeks



Median time-to-onset (range/IQR), weeks

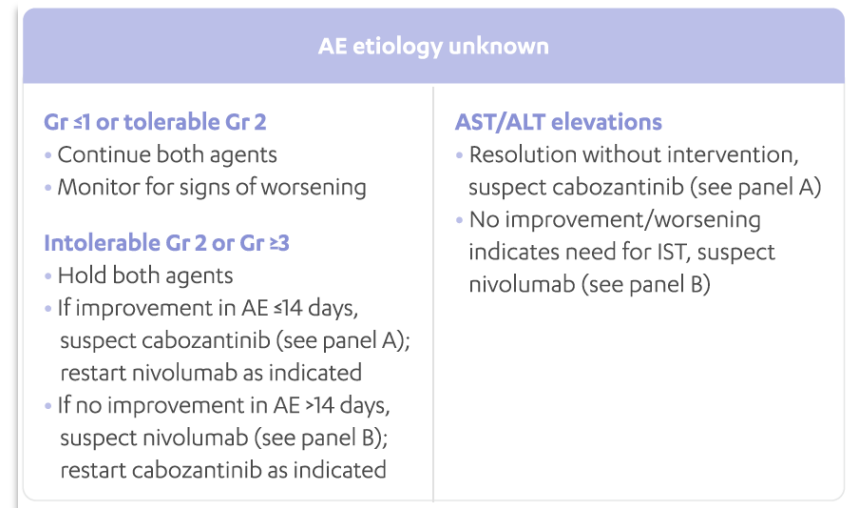
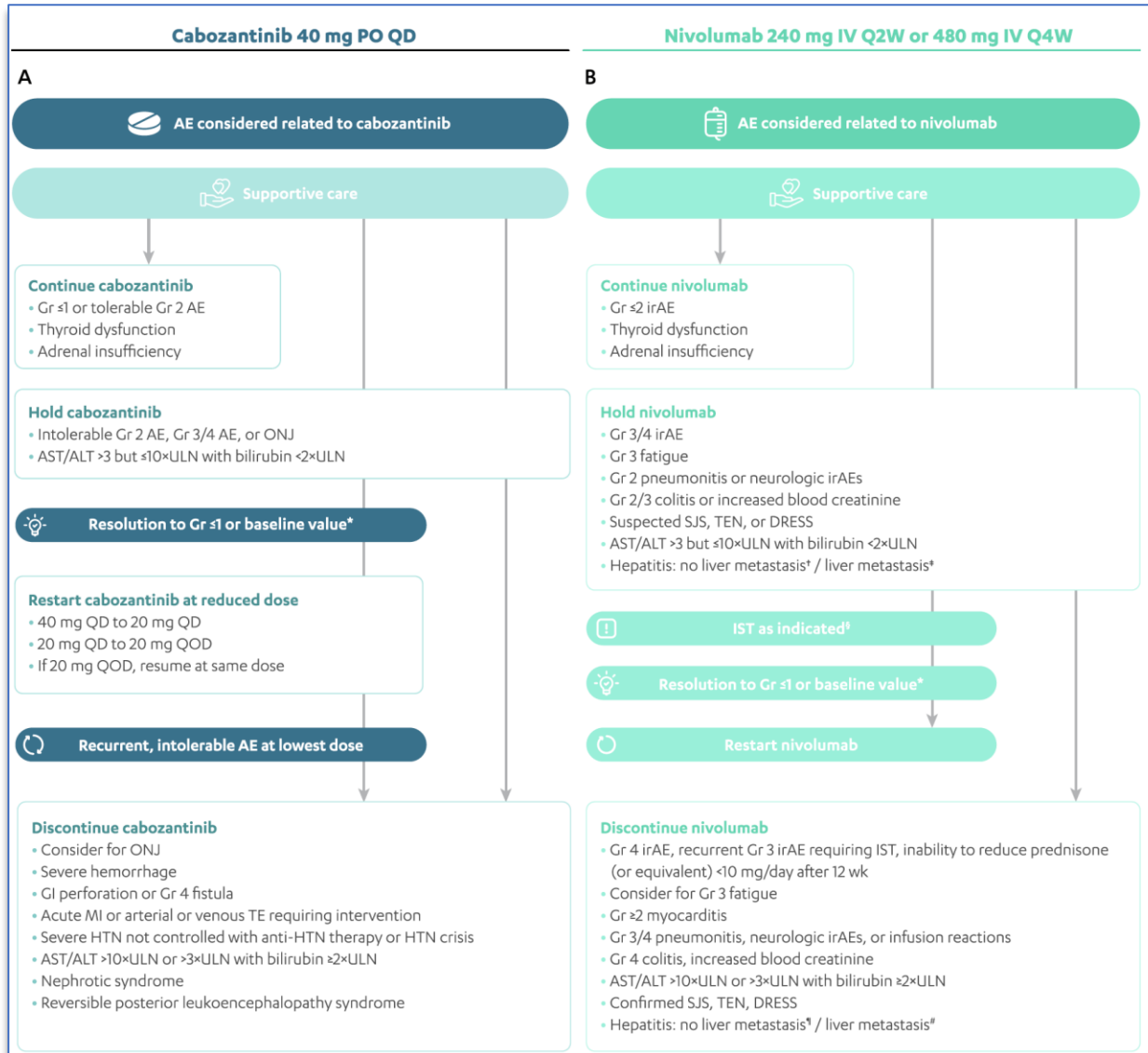


- Cabozantinib+nivolumab (CheckMate 9ER; n=320)
- ◆ Single-agent cabozantinib (METEOR; n=331)
- Single-agent nivolumab (pooled analysis; n=3239)



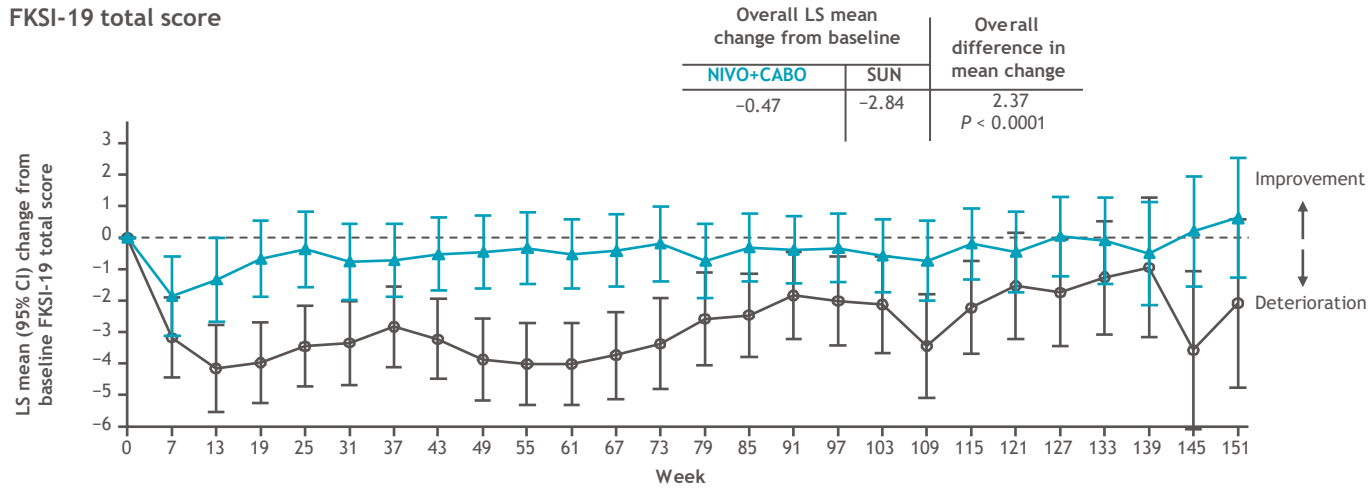
- Associated with cabozantinib+nivolumab
- Associated with cabozantinib
- Associated with nivolumab

Management of AEs with Cabo-Nivo



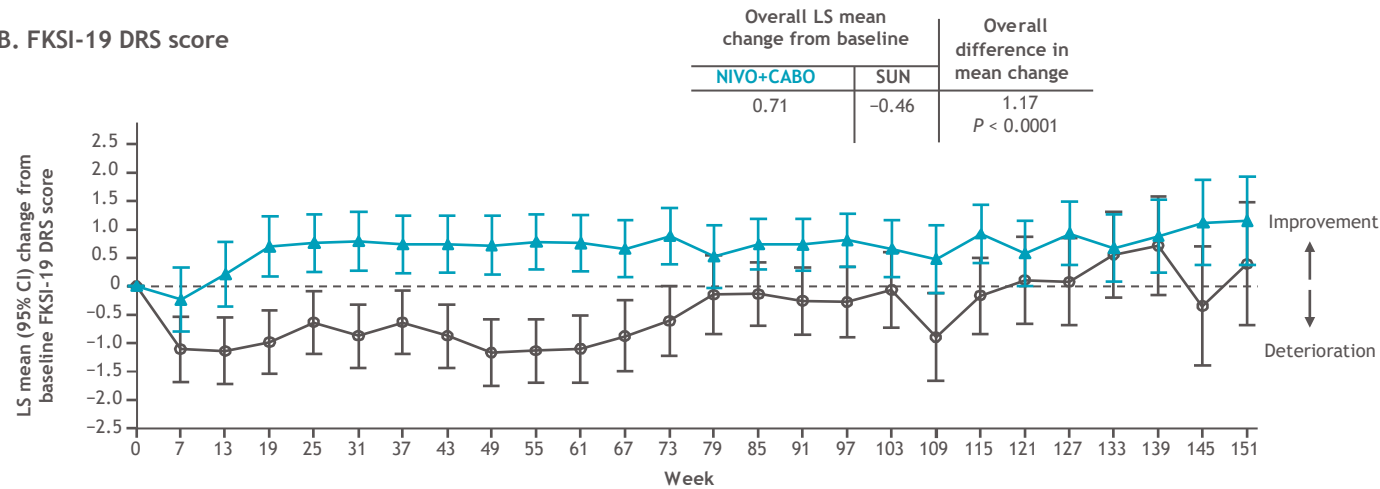
Estimated changes from baseline through week 151 in PRO scores (MMRM analysis)

A. FKSI-19 total score



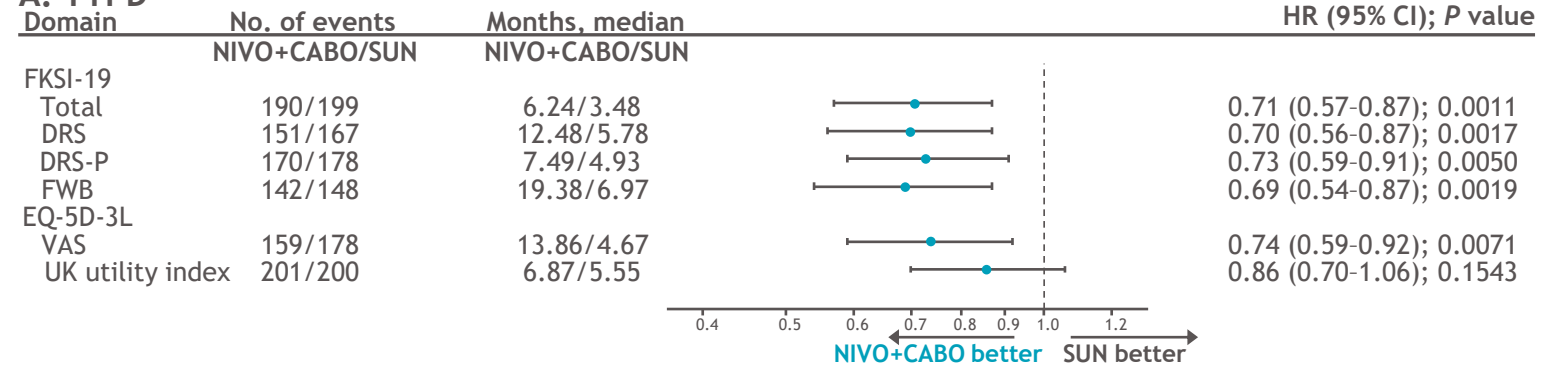
No. at risk	0	7	13	19	25	31	37	43	49	55	61	67	73	79	85	91	97	103	109	115	121	127	133	139	145	151
NIVO+CABO	299	261	246	242	229	217	199	191	178	167	174	171	151	144	138	135	137	126	97	92	77	67	46	34	32	19
SUN	310	262	227	201	179	163	152	143	119	116	99	89	88	79	76	66	64	63	52	50	42	34	27	18	15	10

B. FKSI-19 DRS score

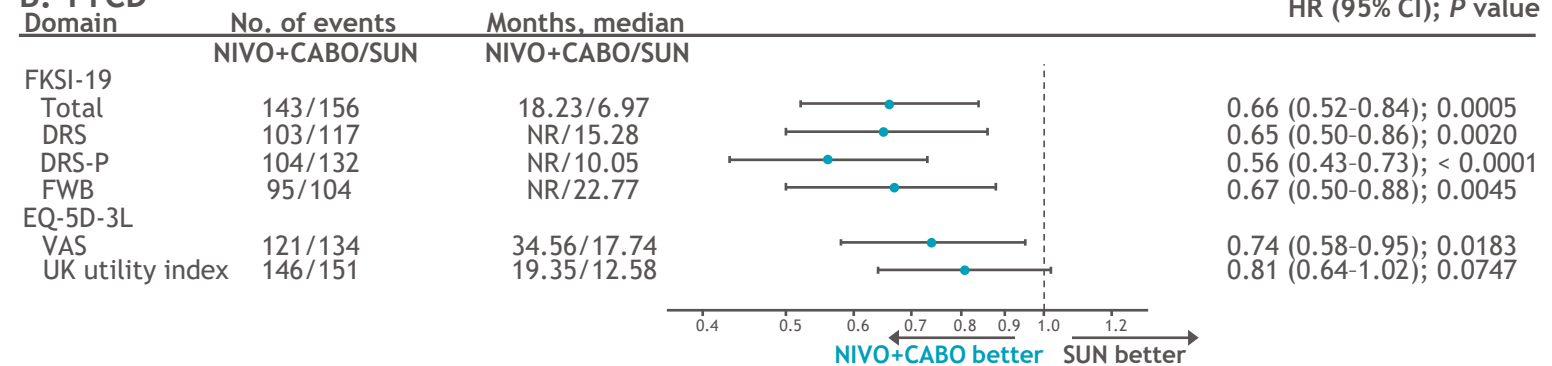


No. at risk	0	7	13	19	25	31	37	43	49	55	61	67	73	79	85	91	97	103	109	115	121	127	133	139	145	151
NIVO+CABO	299	260	246	242	229	217	199	191	178	167	174	171	151	144	138	135	137	126	97	92	77	67	46	34	32	19
SUN	310	262	227	201	178	163	152	143	119	116	99	89	88	79	76	66	64	63	52	50	42	34	27	18	15	10

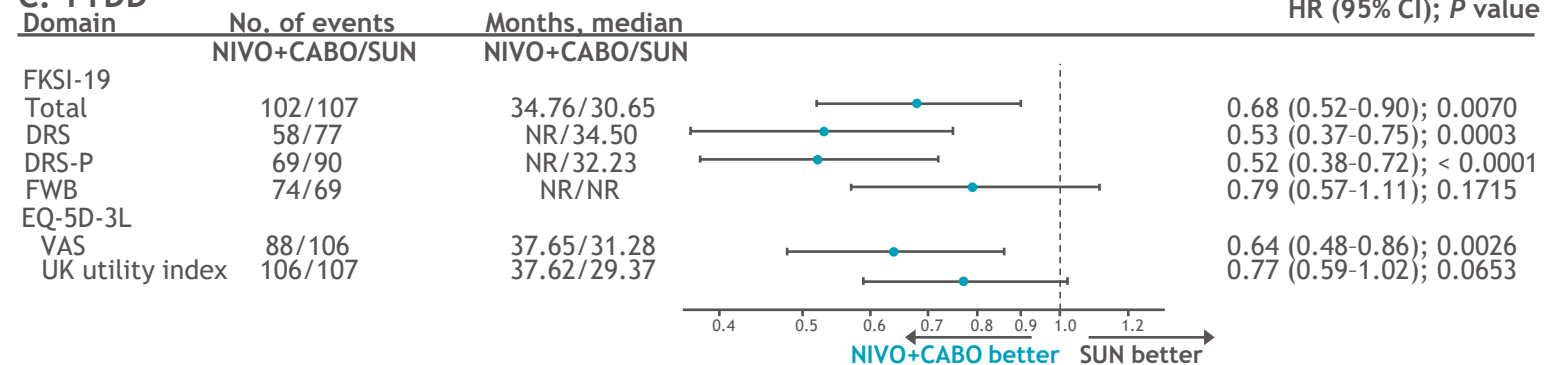
A. TTFD

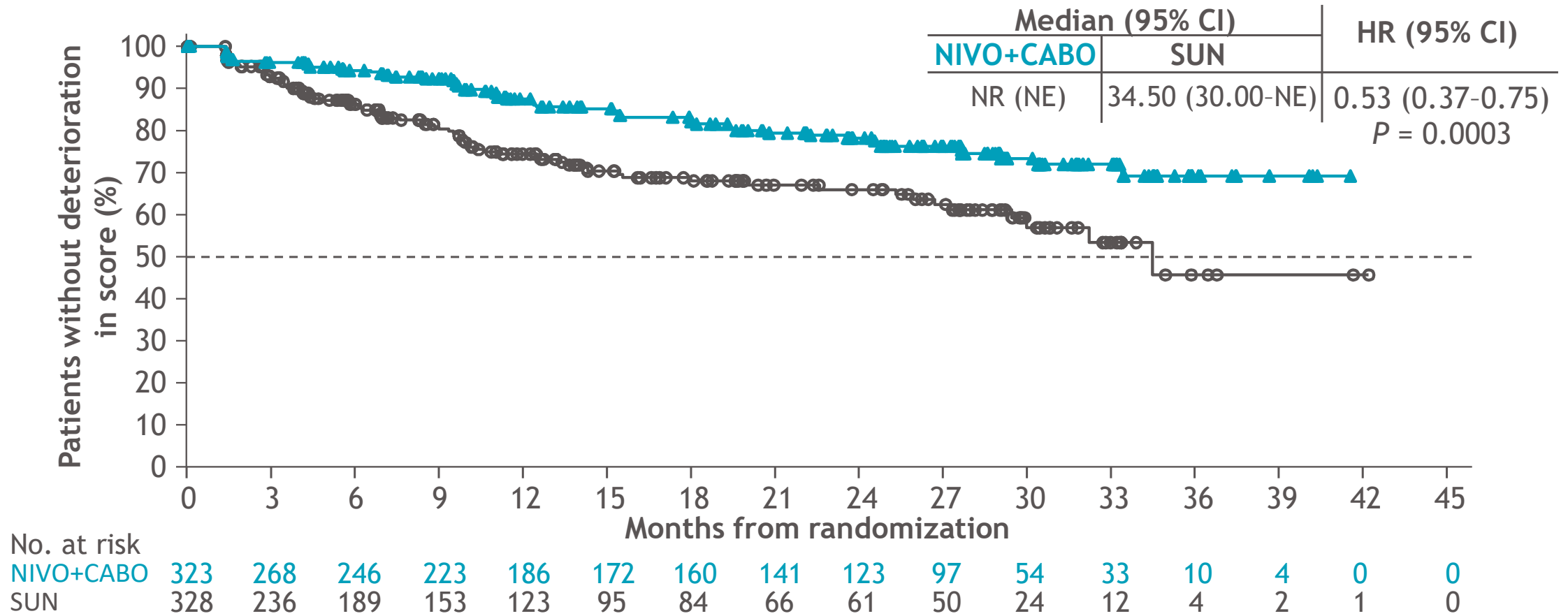


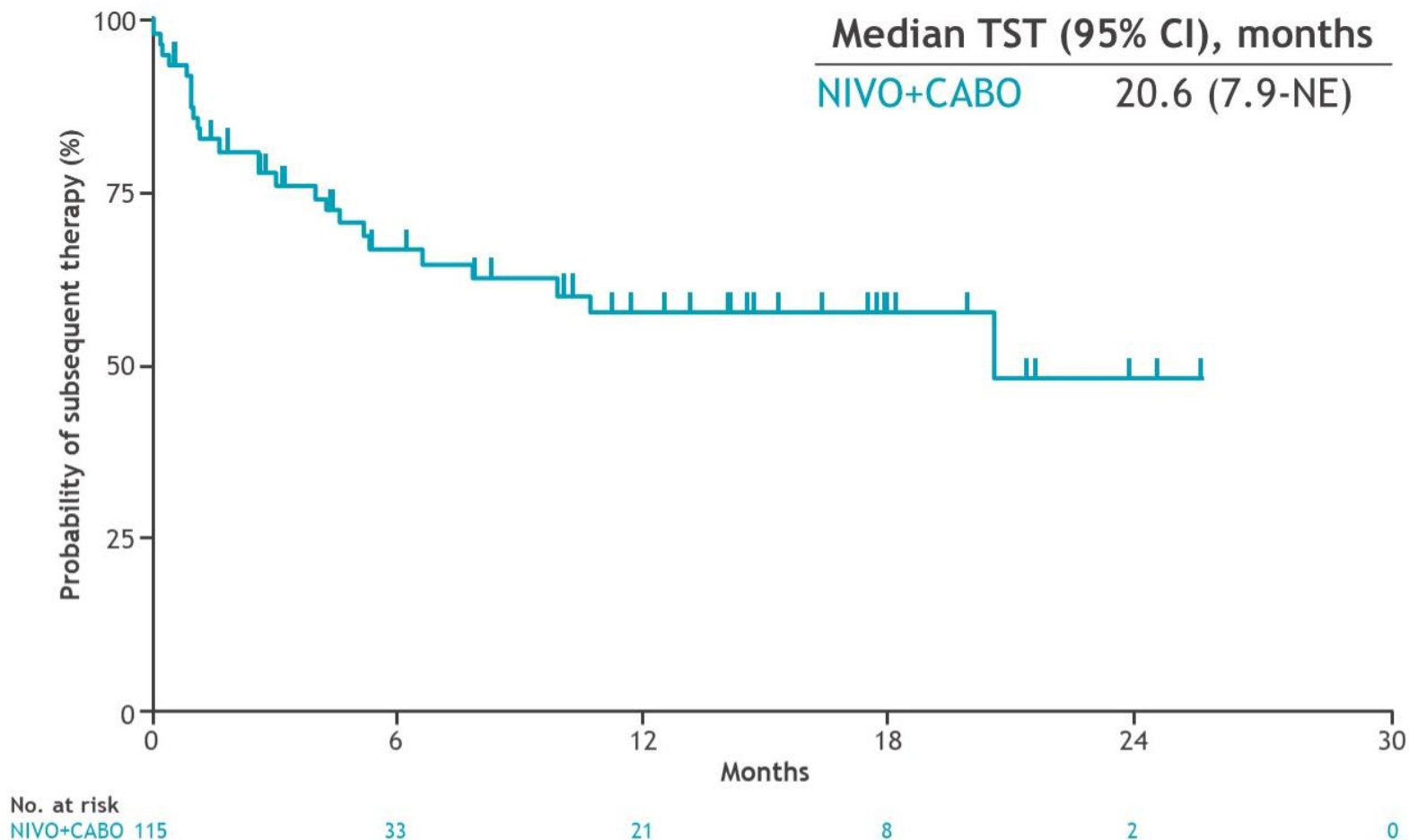
B. TTCD



C. TTDD







TST was defined in patients who have completed 2 years of NIVO treatment, irrespective of continuing or completing treatment with CABO, as (1) the survival time from end of therapy in patients who never received subsequent therapy, and (2) the time from end of therapy until subsequent therapy in patients who received subsequent therapy. An event was defined as receiving subsequent therapy or death. Symbols represent censored observations.

^aAmong patients who discontinued NIVO treatment after 2 years, 101 (88%) continued to receive CABO treatment.

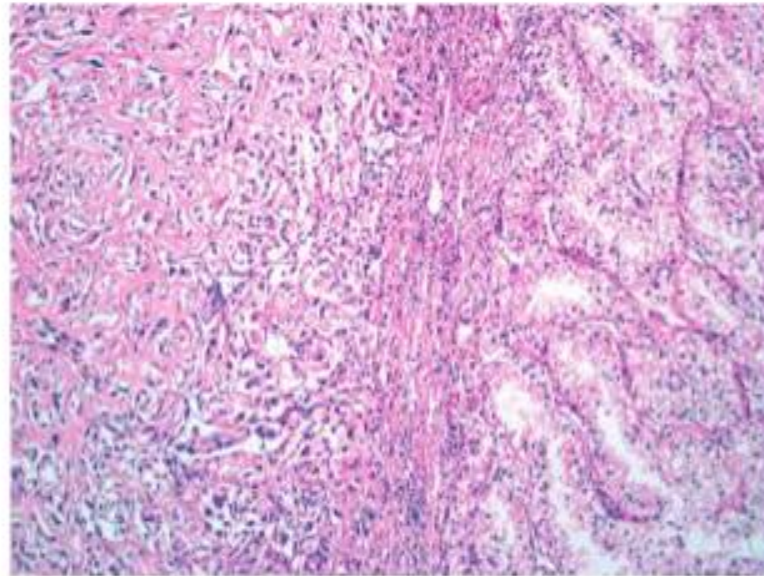
TST, time to subsequent therapy.

- Classic role of Cabozantinib (2L and further lines of therapy)
- Role of cabozantinib in 1L
- **Role of cabozantinib in non-clear cell renal cancer**
- Future of cabozantinib
- Final remarks

Sarcomatoid RCC: subtype of RCC with aggressive behavior



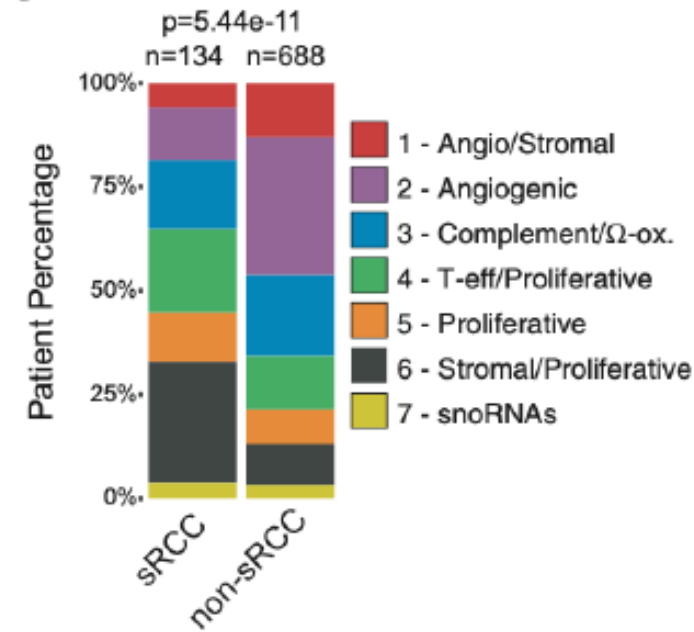
- may occur in any RCC subtype
- represents de-differentiated RCC
- is not a stand-alone entity
- is not a sarcoma



sarcomatoid

clear cell

C



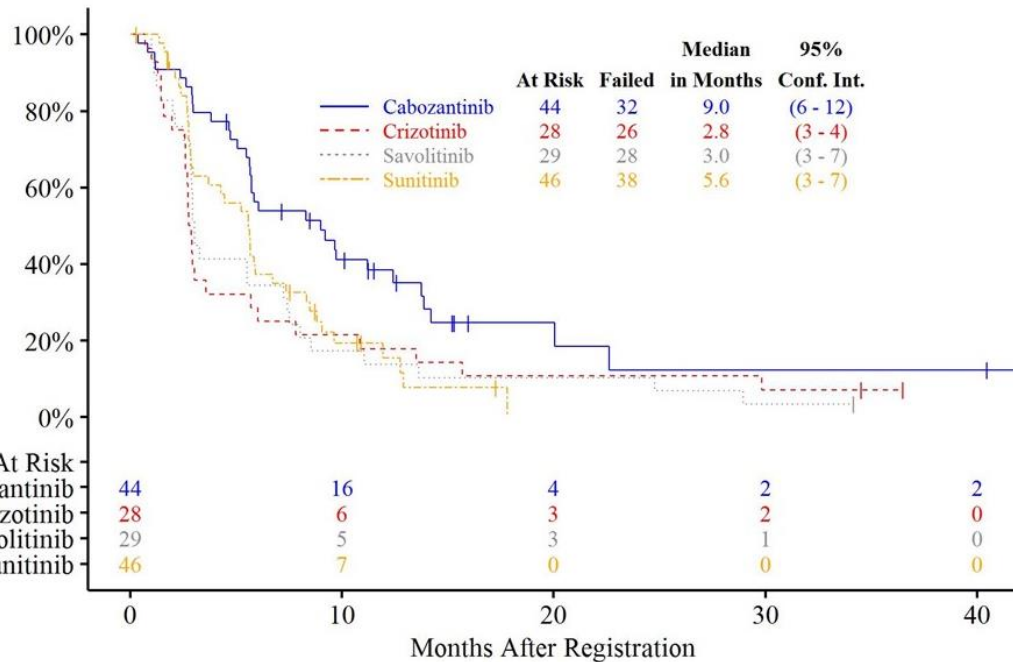
IO-based combos in sarcomatoid mRCC

Trial	Trial Arms	ORR (%)	CR (%)	PFS (mon)	OS (mon)
Checkmate 214* n=139	Nivo-Ipi vs Sunitinib	60.8 vs 23.1 P<0.0001	23 vs 6.2	26.5 vs 5.5	48.6 vs 14.2 P=0.004
Keynote 426* n=105	Pembro-Axi vs Sunitinib	58.8 vs 31.5 NS	11.8 vs 10	NR vs 8.4 NS	12m OS 83.4% vs 79.5%, NS
Checkmate 9ER n=75	Nivo-Cabo vs Sunitinib	55.9 vs 22	8.8 vs 2.4	10.9 vs 4.2 HR0.39 (0.22-0.7)	NR vs 19.7 HR0.36 (0.16-0.82)
JAVELIN 101 n=108	Avelumab-Axi vs Sunitinib	46.8 vs 21.3	4.3 vs 0	7 vs 4 NS	N/A
IMMOTION 151 n=142	Atezo-Bev vs Sunitinib	49 vs 14	10 vs 3	8.3 vs 5.3	21.7 vs 15.4 NS
CLEAR n=49 (P/L vs S)	Pembro-Lenva vs Lenva-Everolimus vs Sunitinib N/A				

Cabozantinib in non-clear cell

Progression-Free Survival

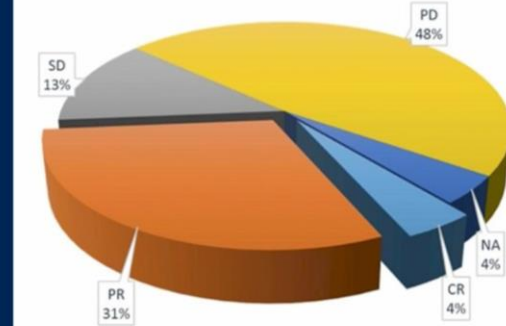
Data as of October 14, 2020



Cabozantinib for Collecting Duct Carcinoma

Summary of Tumor Response

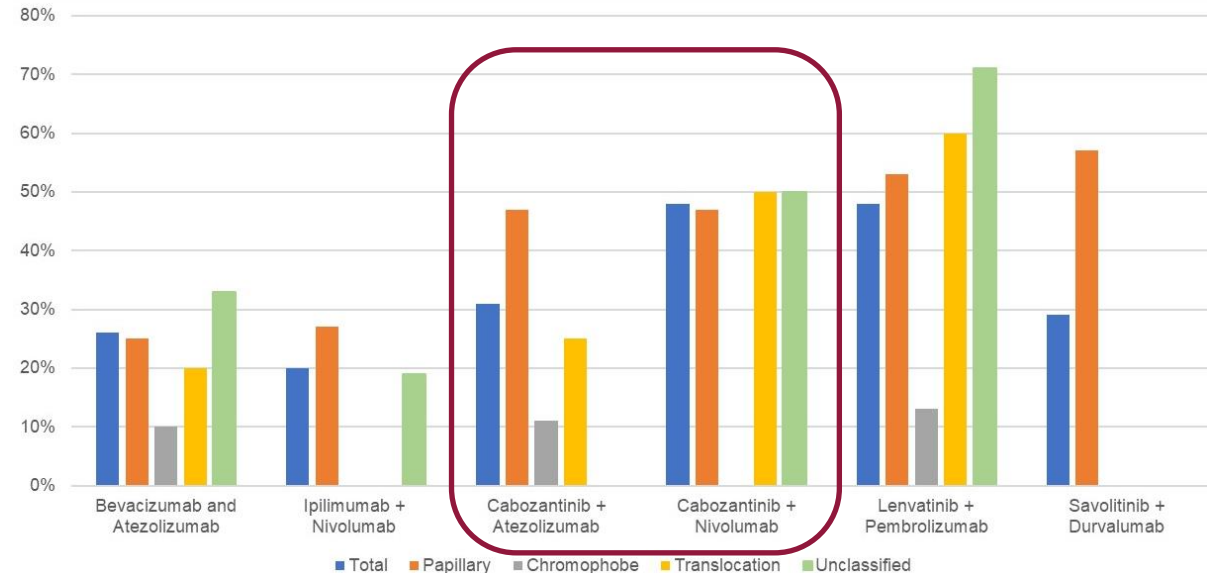
ORR (CR+PR) 35% (8/23)



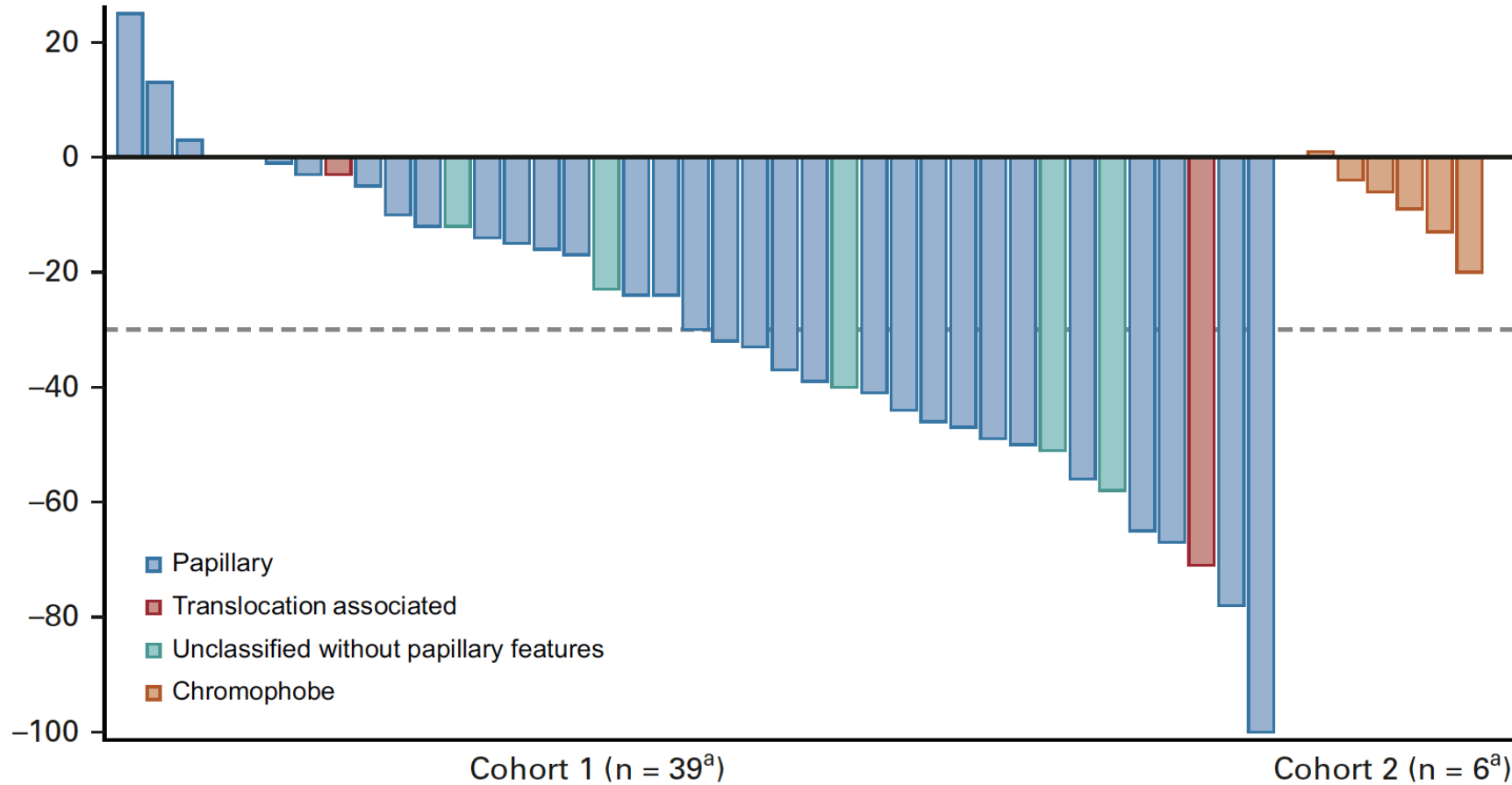
- DNA sequencing (n=21 (91%))
 - All tumors microsatellite stable
 - No association between tumor mutational burden and response
- PFS > 6 months associated with mutations affecting deubiquitination, cell-cell communication, and TGF- β signaling
- Non-responders frequently mutated in chromatin remodeling, transcriptional regulation and WNT pathways

Median PFS was 6 months

Prosenca et al. J Clin Oncol 2022

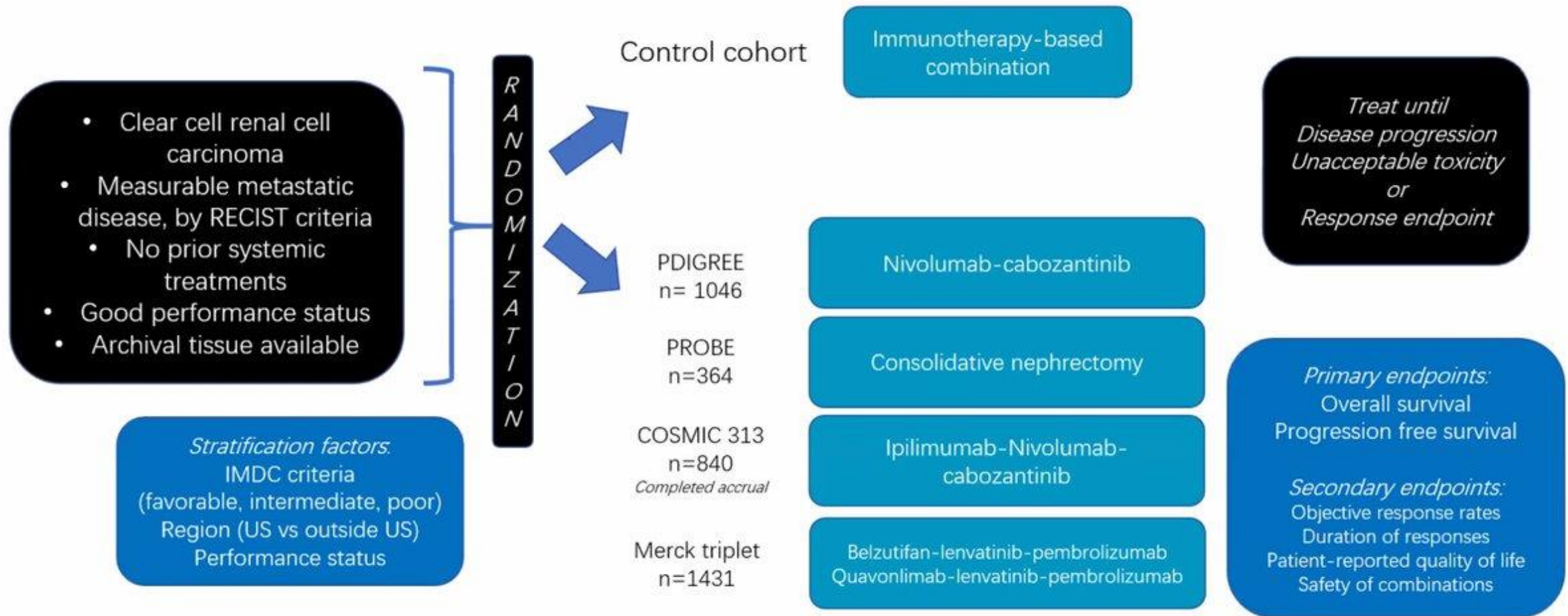


Phase II trial of Cabozantinib plus Nivolumab in non-clear cell

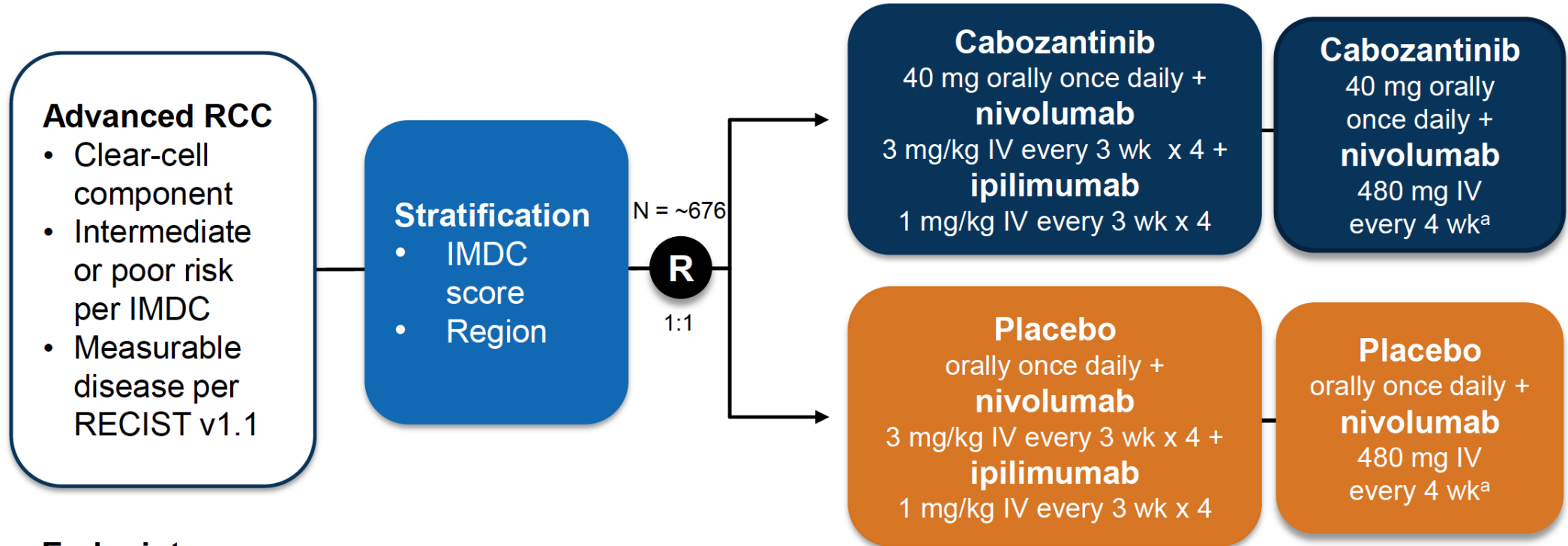


- Classic role of Cabozantinib (2L and further lines of therapy)
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Next Generation 1st-Line phase 3 trials design in mRCC



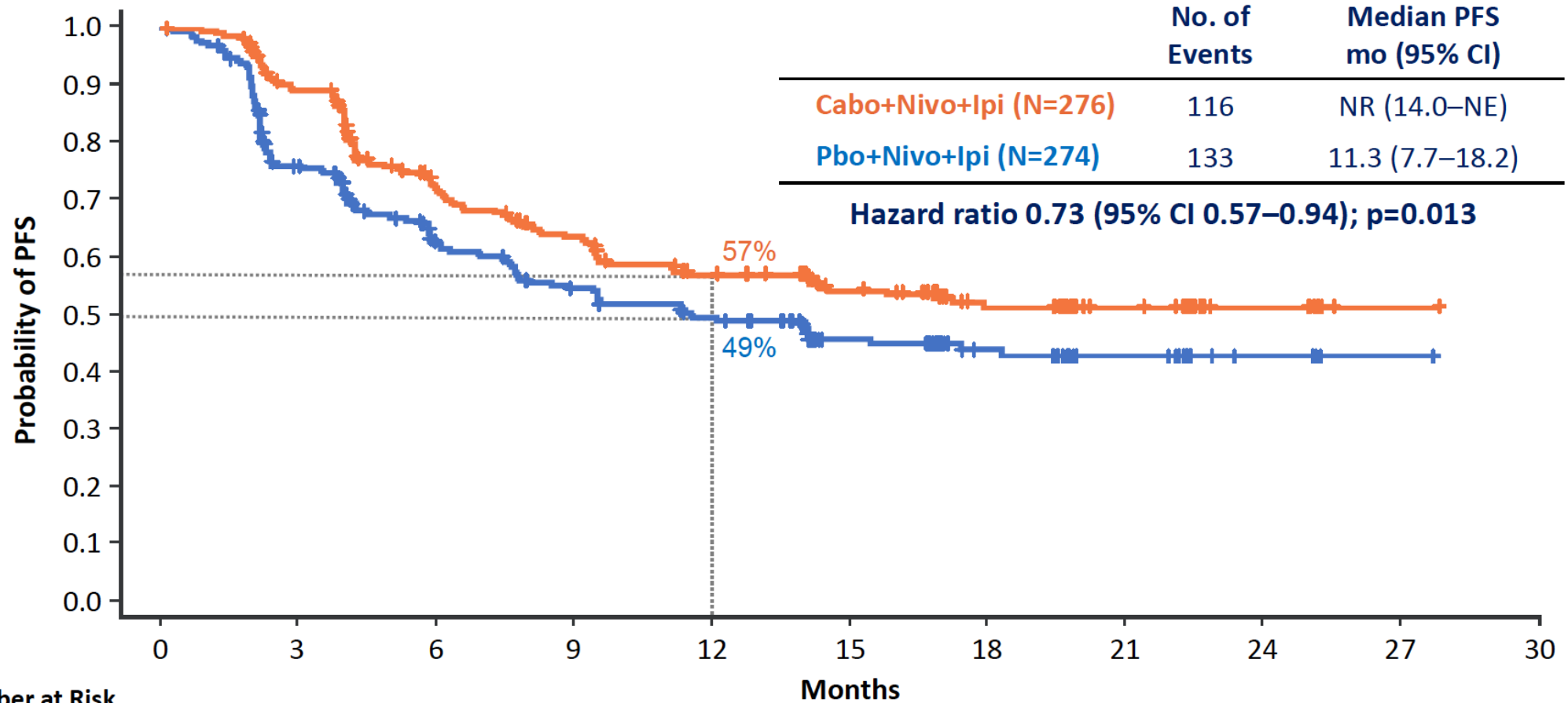
COSMIC 313: Cabozantinib in Combination With Nivolumab and Ipilimumab in Patients with mRCC



Endpoints

- **Primary:** PFS per RECIST 1.1 by BIRC
- **Key secondary:** OS
- Tumor assessment every 8 wk (RECIST v1.1)^b
- Treatment until loss of clinical benefit^c or intolerable toxicity

COSMIC 313: PFS Final Analysis (PITT population)



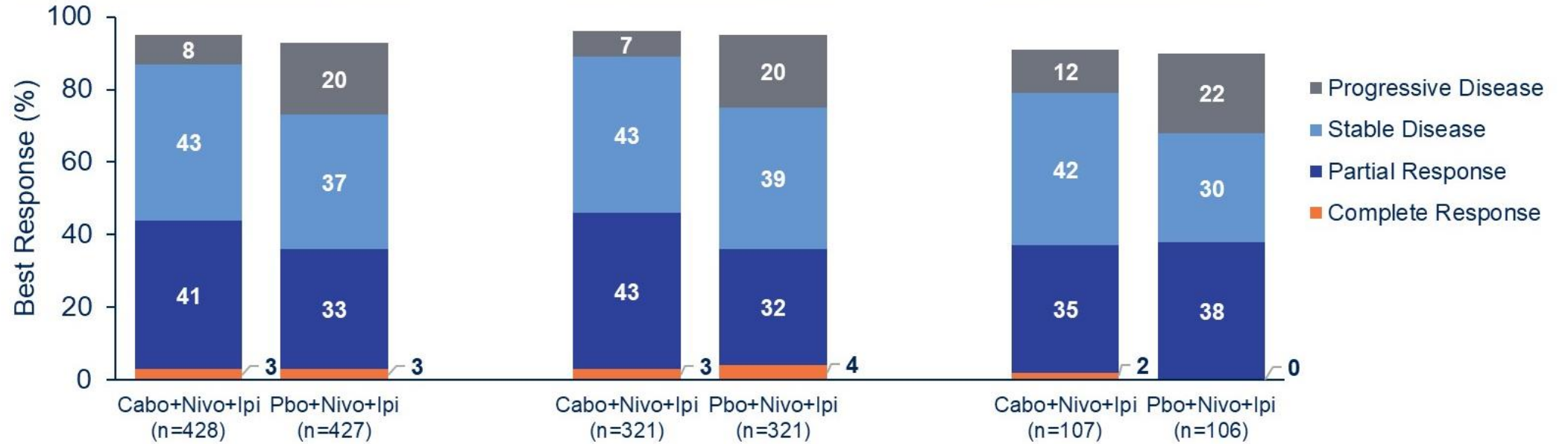
Number at Risk

	0	3	6	9	12	15	18	21	24	27	30
Cabo+Nivo+Ipi	276	234	170	145	119	97	56	33	10	1	0
Pbo+Nivo+Ipi	274	185	136	115	98	69	37	19	5	1	0

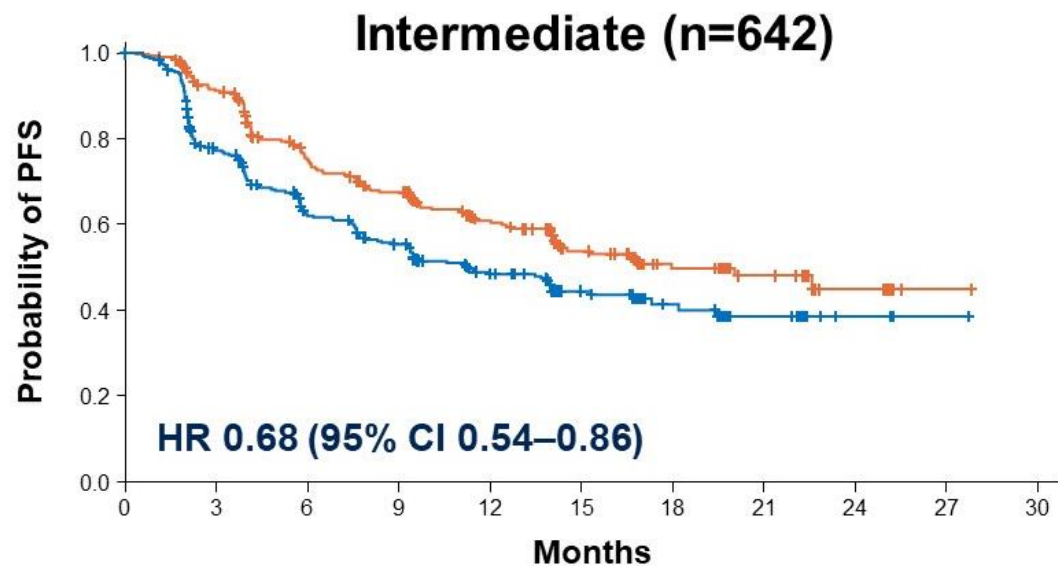
	ITT	
Objective response rate, %	43	36
Disease control rate, %	86	73

	Intermediate risk	
Objective response rate, %	45	36
Disease control rate, %	88	74

	Poor risk	
Objective response rate, %	36	38
Disease control rate, %	79	68

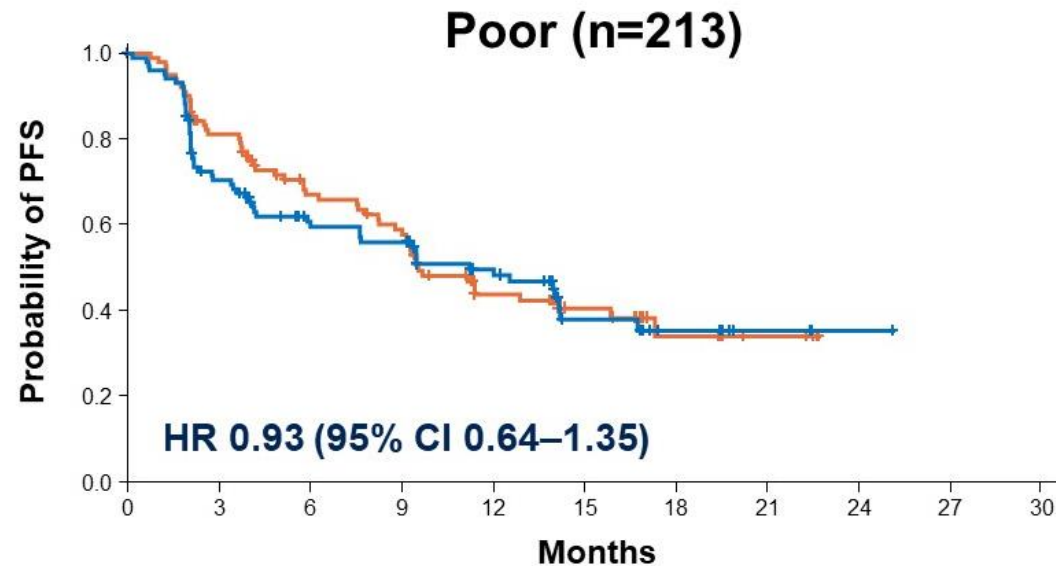


A 32% reduction in the risk of progression or death was observed with the triplet regimen compared with the control in the intermediate risk



Cabo + Nivo + Ipi	321	278	211	182	133	81	48	28	10	1	0
Pbo + Nivo + Ipi	321	226	170	146	105	57	30	16	4	1	0

	n	No. of events	Median PFS, mo (95% CI)
Cabo + Nivo + Ipi	321	131	17.9 (14.1–NE)
Pbo + Nivo + Ipi	321	161	11.3 (8.4–15.3)



Cabo + Nivo + Ipi	107	79	58	50	29	18	8	5	0	0
Pbo + Nivo + Ipi	106	69	51	47	35	14	7	3	1	0

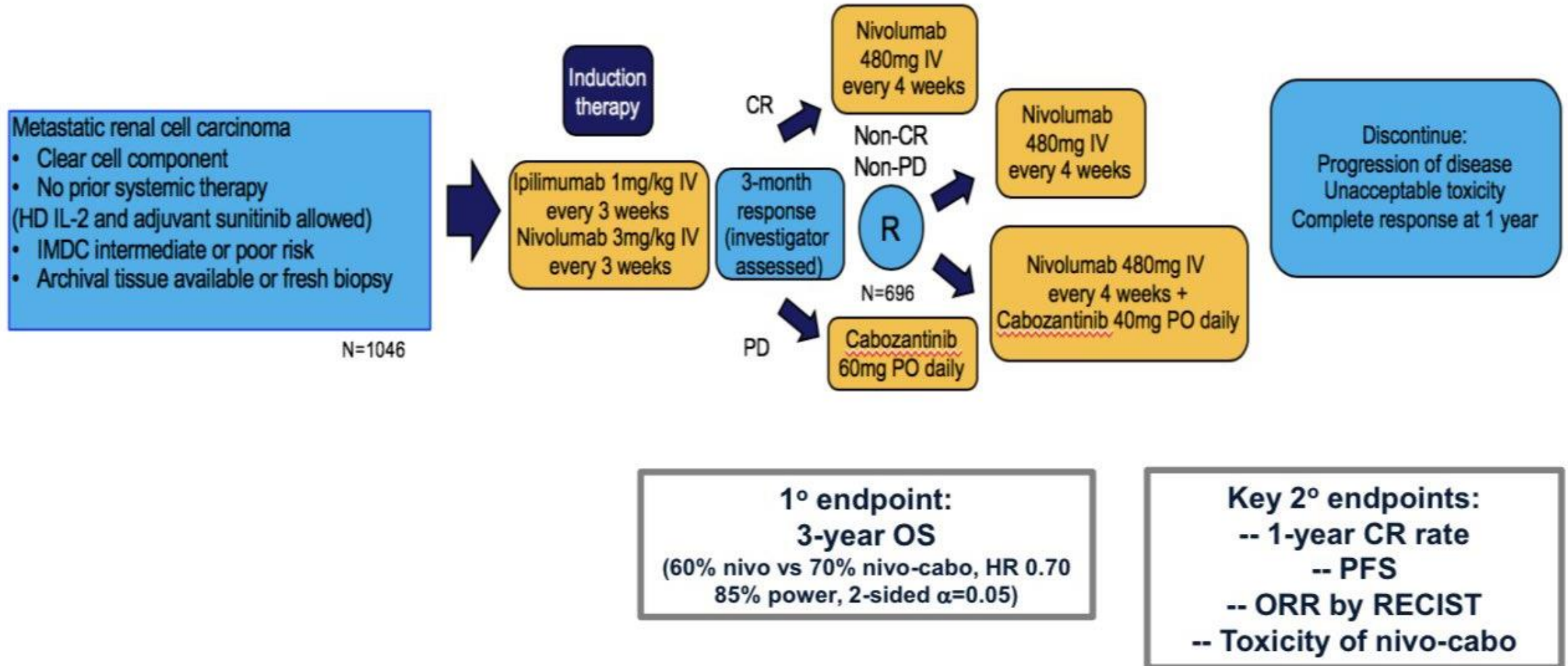
	n	No. of events	Median PFS, mo (95% CI)
Cabo + Nivo + Ipi	107	55	9.5 (8.3–15.8)
Pbo + Nivo + Ipi	106	55	11.2 (6.0–14.2)

Median follow-up of 17.7 mo; total of 855 patients and 402 PFS events per RECIST 1.1 by BIRC at data cutoff of January 31, 2022.

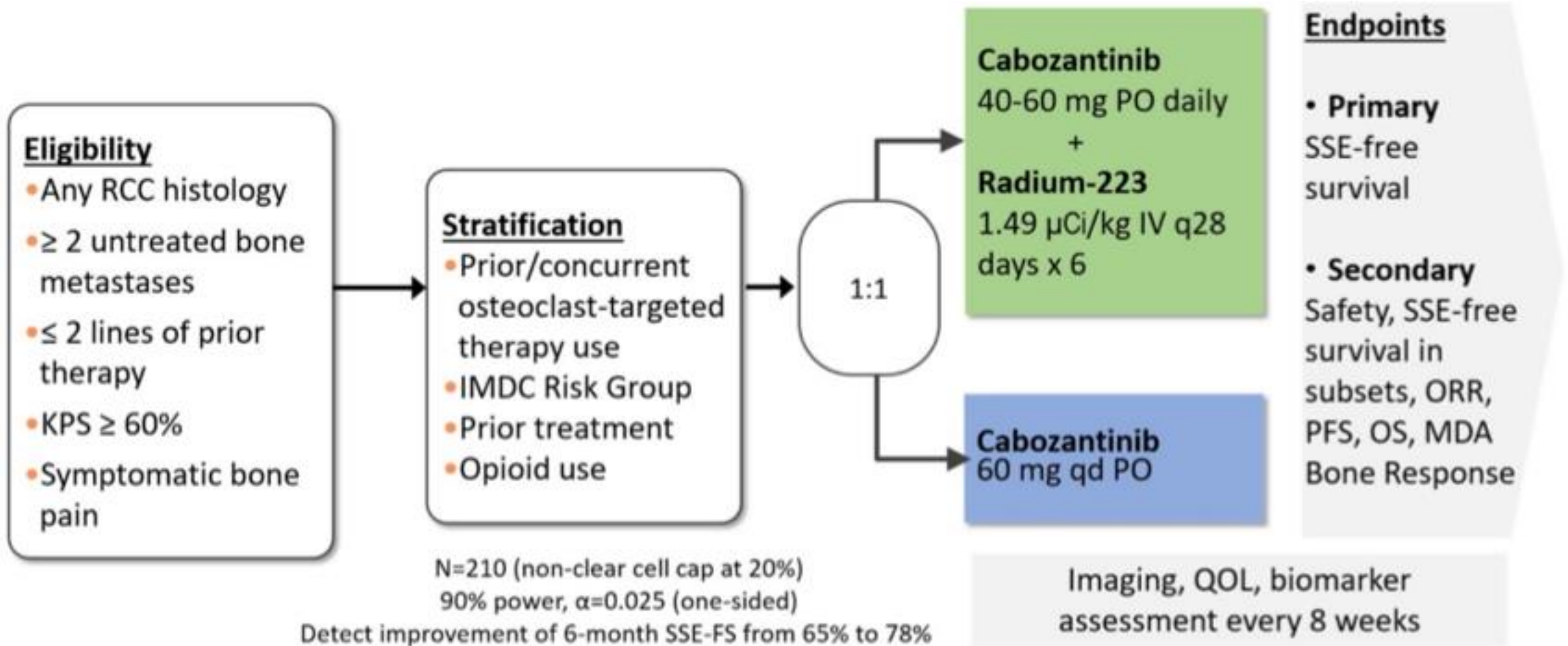
Treatment Exposure and Discontinuation

	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

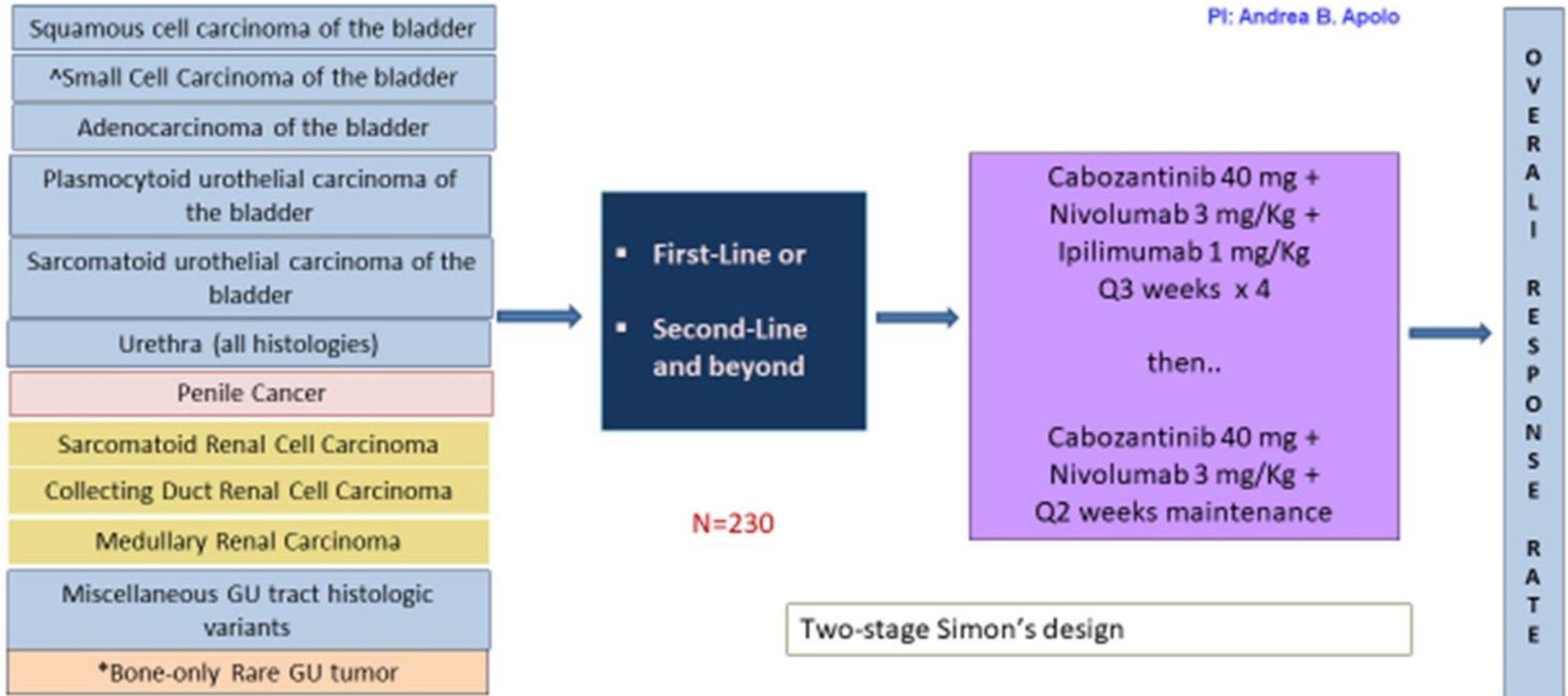
PDIGREE (A031704) study design



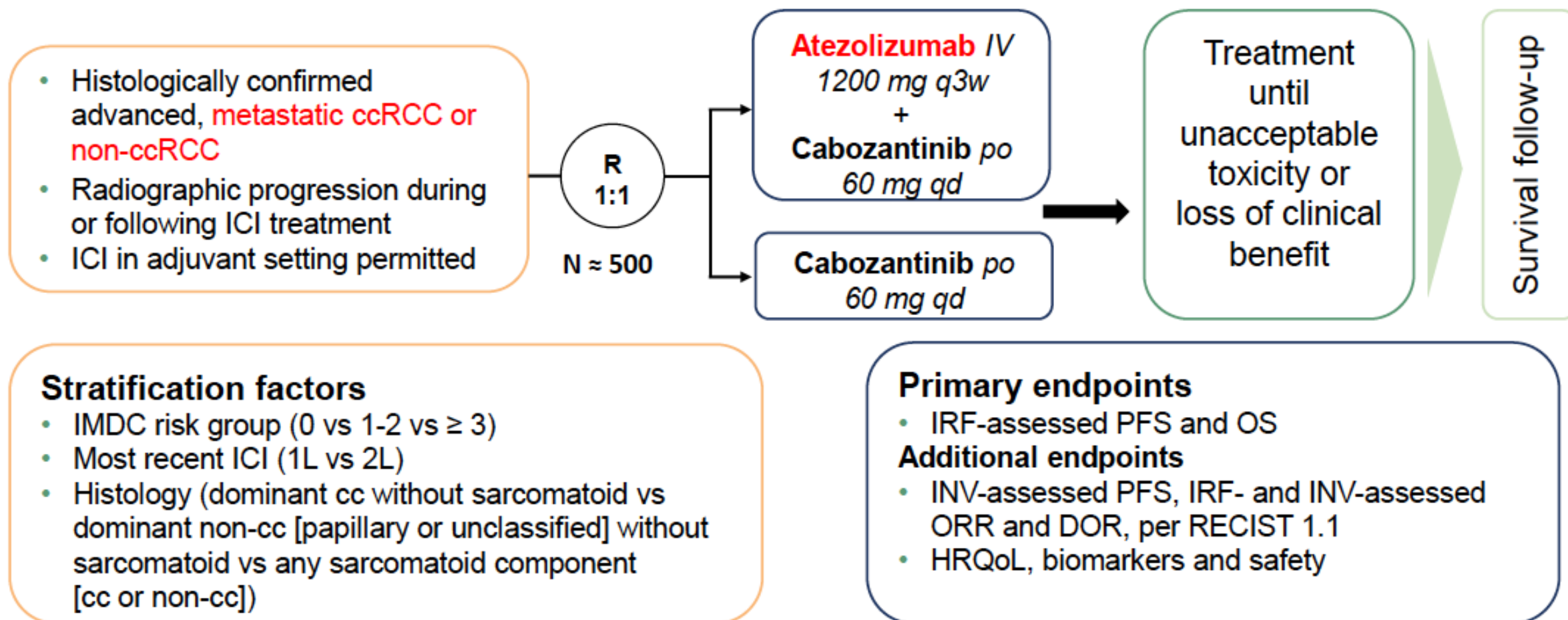
RADICAL (A031801) study design



ICONIC study of Ipilimumab + CabOzantinib + Nivolumab in rare GU Cancers

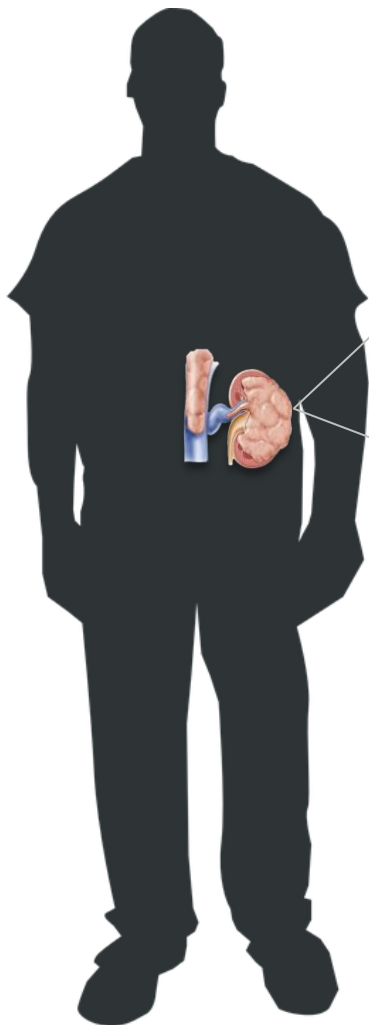


2nd Line: CONTACT-03 (completed phase 3)



- Classic role of Cabozantinib (2L and further lines of therapy)
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- Role of cabozantinib in non-clear cell renal cancer
- Future of cabozantinib
- **Final remarks**

Systemic options for mRCC upfront treatment



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023 Kidney Cancer

[NCCN Guidelines Index](#)
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[Discussion](#)

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Favorable ^a	<ul style="list-style-type: none"> • Axitinib + pembrolizumab^b (category 1) • Cabozantinib + nivolumab^b (category 1) • Lenvatinib + pembrolizumab^b (category 1) 	<ul style="list-style-type: none"> • Axitinib + avelumab^b • Cabozantinib (category 2B) • Ipilimumab + nivolumab^b • Pazopanib • Sunitinib 	<ul style="list-style-type: none"> • Active surveillance^c • Axitinib (category 2B) • High-dose IL-2^d (category 2B)
Poor/intermediate ^a	<ul style="list-style-type: none"> • Axitinib + pembrolizumab^b (category 1) • Cabozantinib + nivolumab^b (category 1) • Ipilimumab + nivolumab^b (category 1) • Lenvatinib + pembrolizumab^b (category 1) • Cabozantinib 	<ul style="list-style-type: none"> • Axitinib + avelumab^b • Pazopanib • Sunitinib 	<ul style="list-style-type: none"> • Axitinib (category 2B) • High-dose IL-2^d (category 3) • Temezirolimus^e (category 3)

IO + IO

Nivolumab + Ipilimumab

Axitinib + Pembrolizumab

Cabozantinib + Nivolumab

TKI + IO

Axitinib + Avelumab

Lenvatinib + Pembrolizumab

More conservative or budget conditioned

TKI alone

Active surveillance



Adapted from Powles T, et al. Ann Oncol 2021

<https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1440>

Factors conditioning upfront treatment to metastatic renal cancer

Patient dependent:

- IMDC criteria
- Age
- Comorbidities
- Toxicity profile

Others:

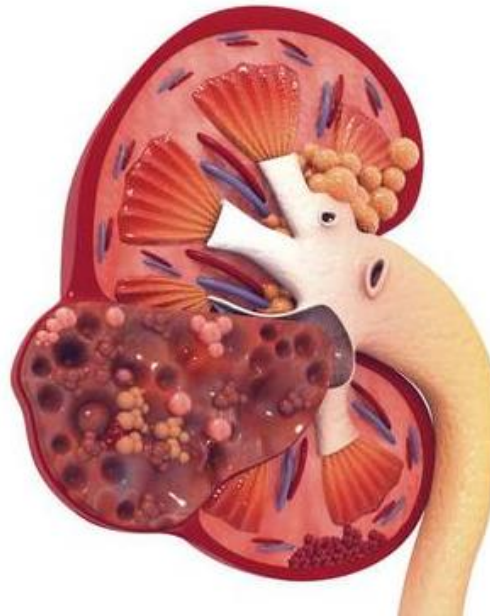
- Access
- Sequential therapies
- Patient's preference

Volumen Disease:

- Location of metastases
- Tumor burden
- Size of primary tumor
- Symptomatic vs asymptomatic

Biology of the disease:

- PDL1 expression, TILs
- Histology (clearcell vs non-clearcell)
- Sarcomatoid features
- Molecular signature
- PBRMI, BAP1 mutation



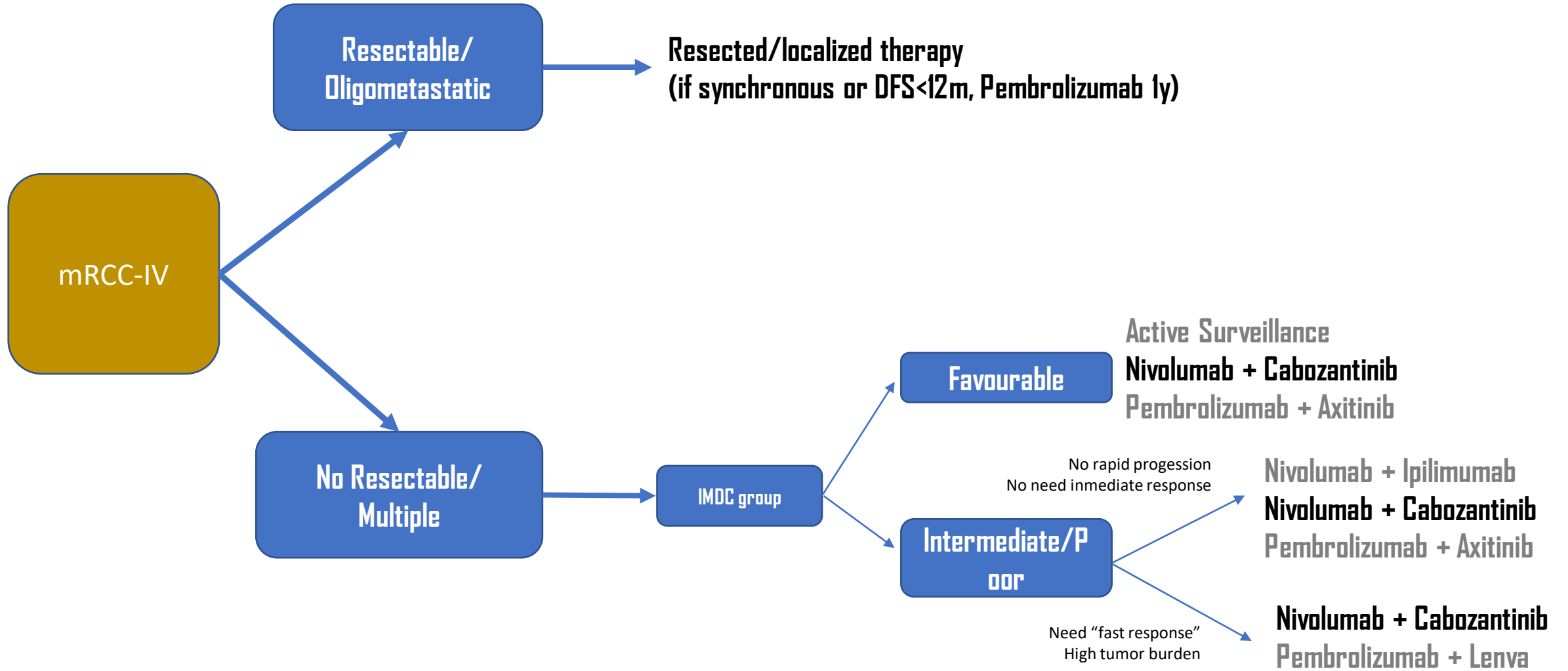
Metastasectomy

Active Surveillance

Cytoreductive nephrectomy

IO/Tki vs Tki vs IO/IO

My own treatment decision in 1st line mRCC





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