Treatment of RCC in 2023: An Update for Medical Oncologists

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Key Trials in the Adjuvant Space

KEYNOTE-564

Key Eligibility Criteria
- Histologically confirmed clear cell renal cell carcinoma
  - pT2, grade 4 or sarcomatoid, N0, M0
  - pT3 or pT4, any grade, N0, M0
  - Any pT, any grade, N+, M0
  - M1 no evidence of disease (NED) after surgery
- Surgery ≤12 weeks prior to randomization
- No prior systemic therapy
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment

Stratification Factors
- Metastatic status (M0 vs M1 NED)
- M0 group further stratified:
  - ECOG PS 0 vs 1
  - US vs non-US

R (1:1)

- Pembrolizumab 200 mg Q3W for ~1 year[a]
- Placebo Q3W for ~1 year[a]

- Primary endpoint: DFS per investigator
- Key secondary endpoint: OS
- Other secondary endpoints: Safety, PROs

Immotion010

Key eligibility criteria
- Resected intermediate- to high-risk[a] RCC
  - T2 Grade 4
  - T3a Grade 3/4
  - T3b/c or T4 any Grade
  - TXN+ any Grade
  - M1 NED[b]
- Clear cell and/or sarcomatoid component

R 1:1
N=778

- Atezolizumab 1200 mg IV q3w for 16 cycles or 1 year[c]
- Placebo IV q3w for 16 cycles or 1 year[c]

Stratification factors
- **Disease stage** (T2/T3a vs T3b/c/T4/N+ vs M1 NED)
- **PD-L1 expression on IC[d]** (IC0 [<1%] vs IC1/2/3 [≥1%])
- **Region** (North America[e] vs rest of world)

Primary endpoint
- Investigator-assessed DFS in ITT population

Key secondary endpoints
- OS in the ITT population
- Investigator-assessed DFS in the IC1/2/3 population
- IRF-assessed DFS in the ITT and IC1/2/3 populations
- IRF-assessed EFS in the ITT population
- Safety

CheckMate 914

N = 816

Key inclusion criteria[1]
- Radical or partial nephrectomy with negative surgical margins
- Predominant clear cell histology, including sarcomatoid features
- Pathologic TNM staging:
  - pT2a, G3 or G4, N0 M0
  - pT2b, G any, N0 M0
  - pT3, G any, N0 M0
  - pT4, G any, N0 M0
  - pT any, G any, N1 M0
- No clinical/radiological evidence of residual disease or distant metastases after nephrectomy, confirmed by BICR
- ECOG performance status of 0-1

Stratification factors:
- Pathologic TNM staging[a]
- Type of nephrectomy

R 1:1

Randomization > 4 weeks but ≤ 12 weeks after surgery

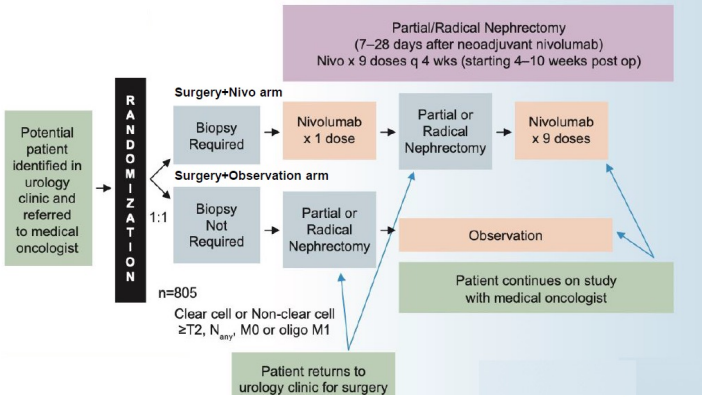
Expected treatment duration of 24 weeks[b]

- **NIVO** 240 mg IV Q2W (× 12 doses) + **IPI** 1 mg/kg IV Q6W (× 4 doses) N = 405
- **Placebo** IV Q2W (× 12 doses) + **Placebo** IV Q6W (× 4 doses) N = 411

Primary endpoint: DFS by BICR

Secondary endpoints: OS and safety

ECOG PROSPER



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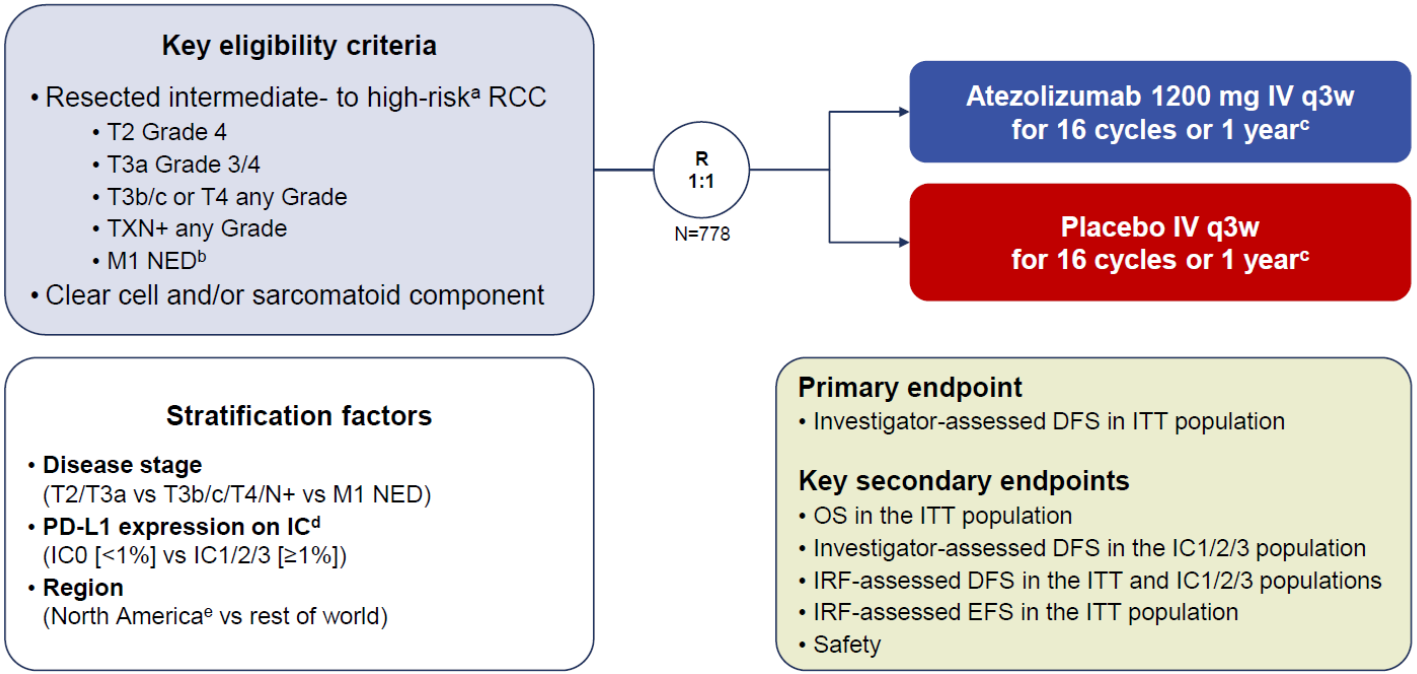

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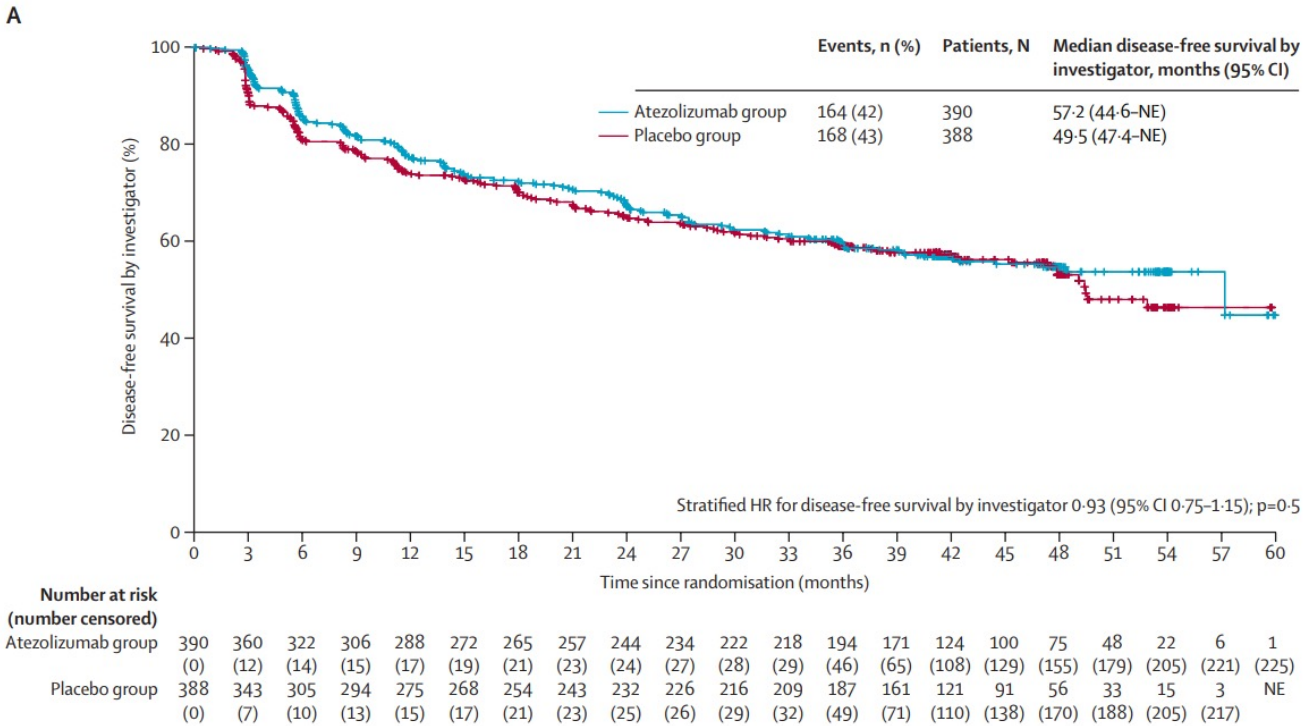

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	Events (n)/patients (N)		Median disease-free survival, months (95% CI)		HR (95% CI)
	Atezolizumab	Placebo	Atezolizumab	Placebo	
All patients	164/390	168/388	57·2 (44·6 to NE)	49·5 (47·4 to NE)	0·93 (0·75–1·15)
Age group , years					
<65	100/248	106/248	57·2 (48·4 to NE)	52·9 (47·4 to NE)	0·91 (0·69–1·19)
≥65	64/142	62/140	42·5 (29·3 to NE)	47·9 (29·4 to NE)	0·96 (0·68–1·36)
Race*					
White	141/324	129/304	57·2 (40·5 to NE)	49·5 (47·4 to NE)	1·00 (0·79–1·27)
Asian	12/43	28/51	NE (NE to NE)	33·1 (8·3 to NE)	0·41 (0·21–0·81)
Black	3/8	1/9	NE (5·6 to NE)	NE (NE to NE)	3·72 (0·38–36·09)
Sex					
Male	129/287	117/278	57·2 (36·1 to NE)	52·9 (47·9 to NE)	1·08 (0·84–1·39)
Female	35/103	51/110	NE (NE to NE)	49·1 (30·9 to NE)	0·61 (0·40–0·94)
Geographical region					
North America†	54/143	50/139	NE (48·4 to NE)	NE (47·9 to NE)	1·00 (0·68–1·47)
Rest of the world	110/247	118/249	57·2 (38·0 to NE)	49·1 (36·5 to NE)	0·90 (0·69–1·17)
Component of sarcomatoid					
Yes	18/37	37/67	NE (11·7 to NE)	23·0 (11·3 to NE)	0·77 (0·44–1·36)
No	146/353	131/321	57·2 (47·1 to NE)	49·6 (47·9 to NE)	1·00 (0·79–1·27)
PD-L1 expression					
IC0	71/158	63/153	NE (31·7 to NE)	52·9 (45·4 to NE)	1·08 (0·77–1·52)
IC1, 2, or 3	93/232	105/235	57·2 (44·6 to NE)	47·9 (38·6 to NE)	0·83 (0·63–1·10)
Disease status					
T2–T3a	87/252	89/248	NE (NE to NE)	NE (49·5 to NE)	0·93 (0·69–1·25)
T3b–c or T4 or N+	42/82	45/88	33·0 (26·3 to NE)	37·6 (18·2 to NE)	0·93 (0·61–1·41)
M1 NED	35/56	34/52	24·8 (14·0 to 47·1)	30·0 (15·9 to 45·4)	0·93 (0·58–1·49)
UISS risk score‡					
Intermediate to high risk	90/240	88/221	NE (NE to NE)	52·9 (49·1 to NE)	0·89 (0·67–1·20)
High risk	39/94	46/115	NE (33·0 to NE)	NE (37·9 to NE)	1·02 (0·67–1·57)
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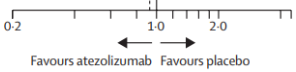

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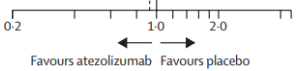

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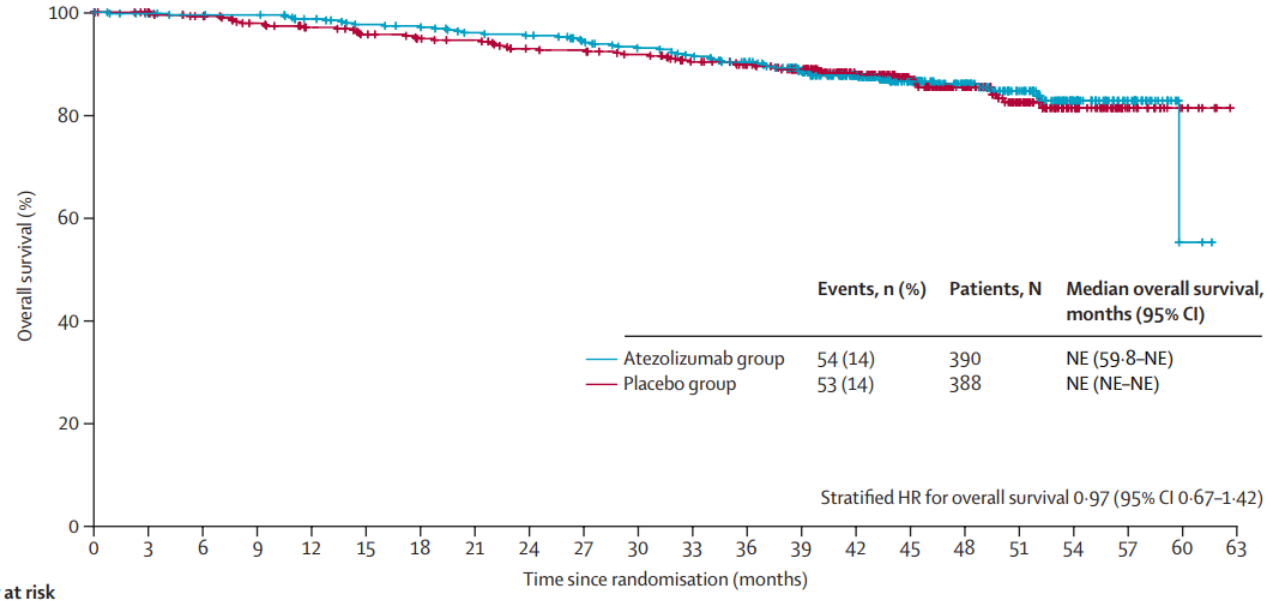

Number at risk (number censored)																						
Atezolizumab group	390	383	379	378	371	365	363	357	355	347	341	336	326	300	250	196	144	103	58	28	2	NE
	(0)	(6)	(9)	(10)	(14)	(16)	(17)	(18)	(18)	(22)	(23)	(23)	(28)	(48)	(95)	(146)	(197)	(236)	(279)	(309)	(334)	
Placebo group	388	379	372	363	355	349	343	340	331	330	325	314	304	287	226	181	138	92	49	20	6	NE
	(0)	(9)	(13)	(17)	(22)	(23)	(26)	(28)	(31)	(31)	(33)	(39)	(47)	(61)	(119)	(163)	(202)	(244)	(286)	(315)	(329)	

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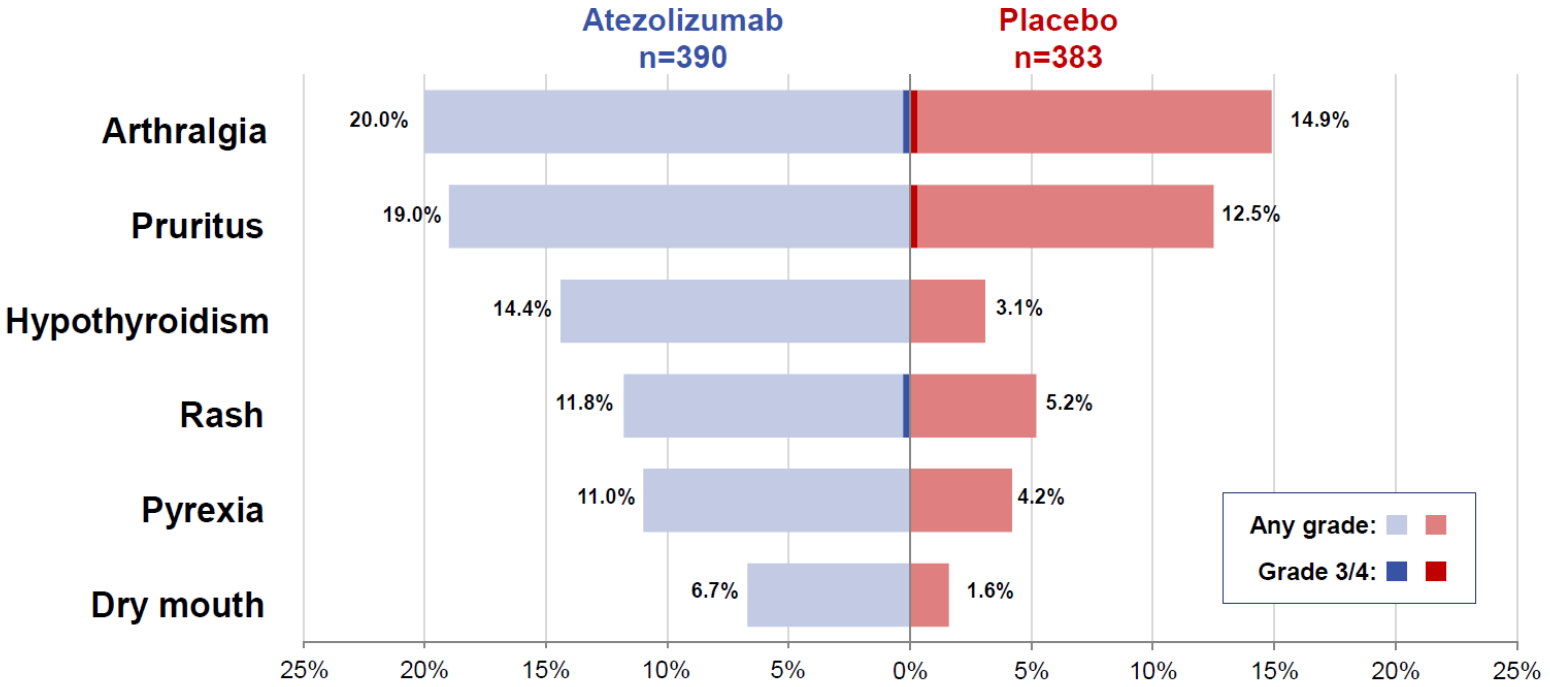

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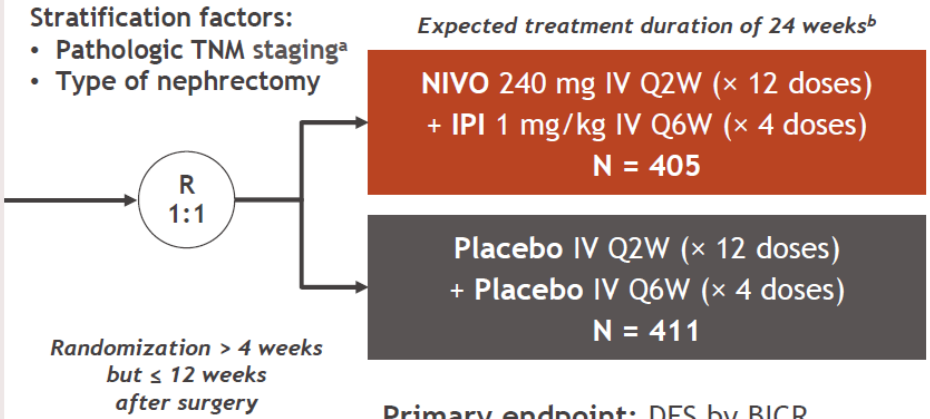
CheckMate-914 (NCT03138512)

N = 816

Key inclusion criteria[1]

- Radical or partial nephrectomy with negative surgical margins
- Predominant clear cell histology, including sarcomatoid features
- Pathologic TNM staging:
  - pT2a, G3 or G4, N0 M0
  - pT2b, G any, N0 M0
  - pT3, G any, N0 M0
  - pT4, G any, N0 M0
  - pT any, G any, N1 M0
- No clinical/radiological evidence of residual disease or distant metastases after nephrectomy, confirmed by BICR
- ECOG performance status of 0-1



Primary endpoint: DFS by BICR

Secondary endpoints: OS and safety

Median (range) study follow-up, 37.0 (15.4-58.0) months

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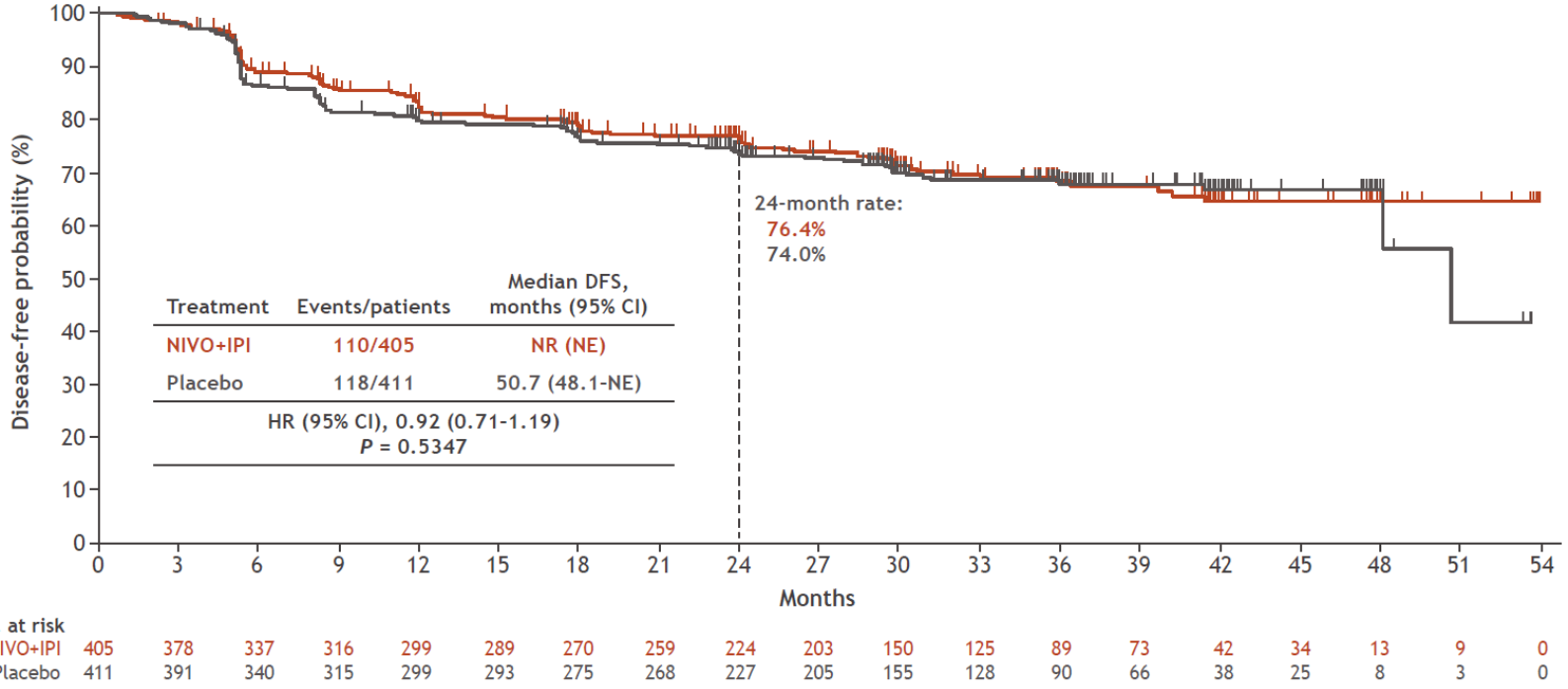

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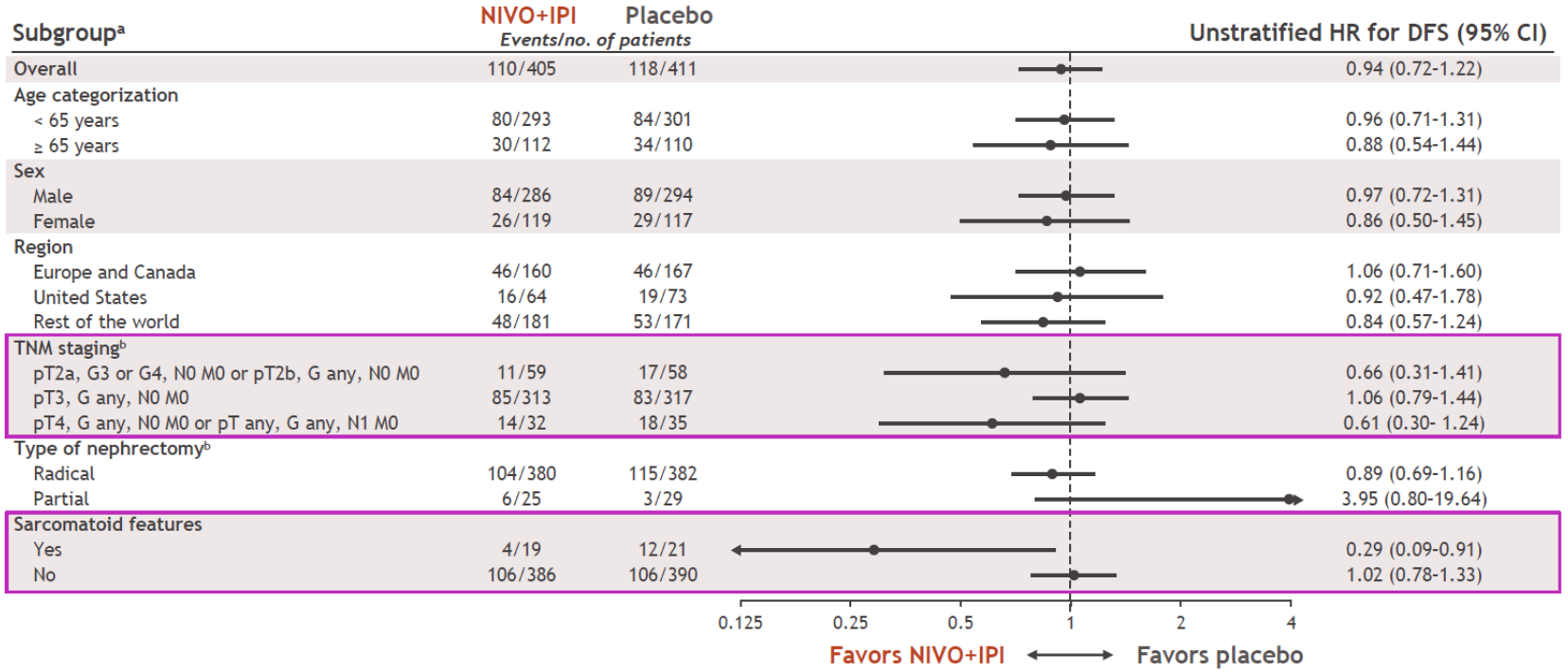

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CheckMate-914 (NCT03138512)

	NIVO+IPI (n = 404)	Placebo (n = 407)
Median duration of therapy (range), months Q1, Q3	**5.1 (< 0.1-8.3)** 2.8, 5.3	**5.1 (< 0.1-8.1)** 5.1, 5.3
Median number of doses received (range)	**NIVO, 12 (1-12)** **IPI, 4 (1-4)**	**12 (1-12)[a]** **4 (1-4)[b]**
Completed all 12/4 doses of NIVO/IPI, n (%)	**231 (57)**	**361 (89)**
Discontinued treatment, n (%)[c] Discontinued due to study drug toxicity, n (%)	**173 (43)** 132 (33)	**46 (11)** 5 (1)
All-cause AEs, n (%)[d] Grade ≥ 3 Led to treatment discontinuation	**392 (97)** 155 (38) 129 (32)	**361 (89)** 42 (10) 9 (2)
Treatment-related AEs, n (%)[d] Grade ≥ 3 Led to treatment discontinuation[e]	**359 (89)** 115 (28) 117 (29)	**231 (57)** 8 (2) 4 (1)
Deaths due to study drug toxicity, n (%)	4 (1)[f]	0

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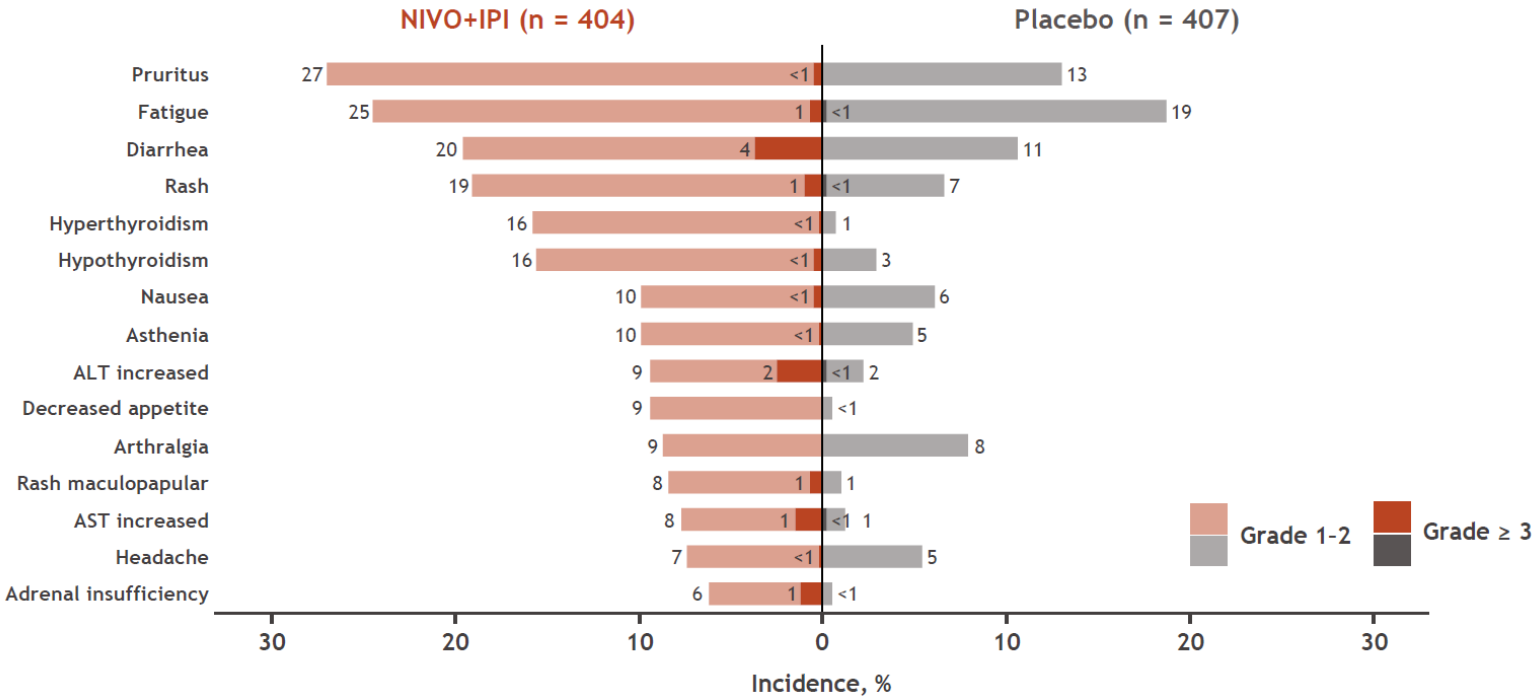

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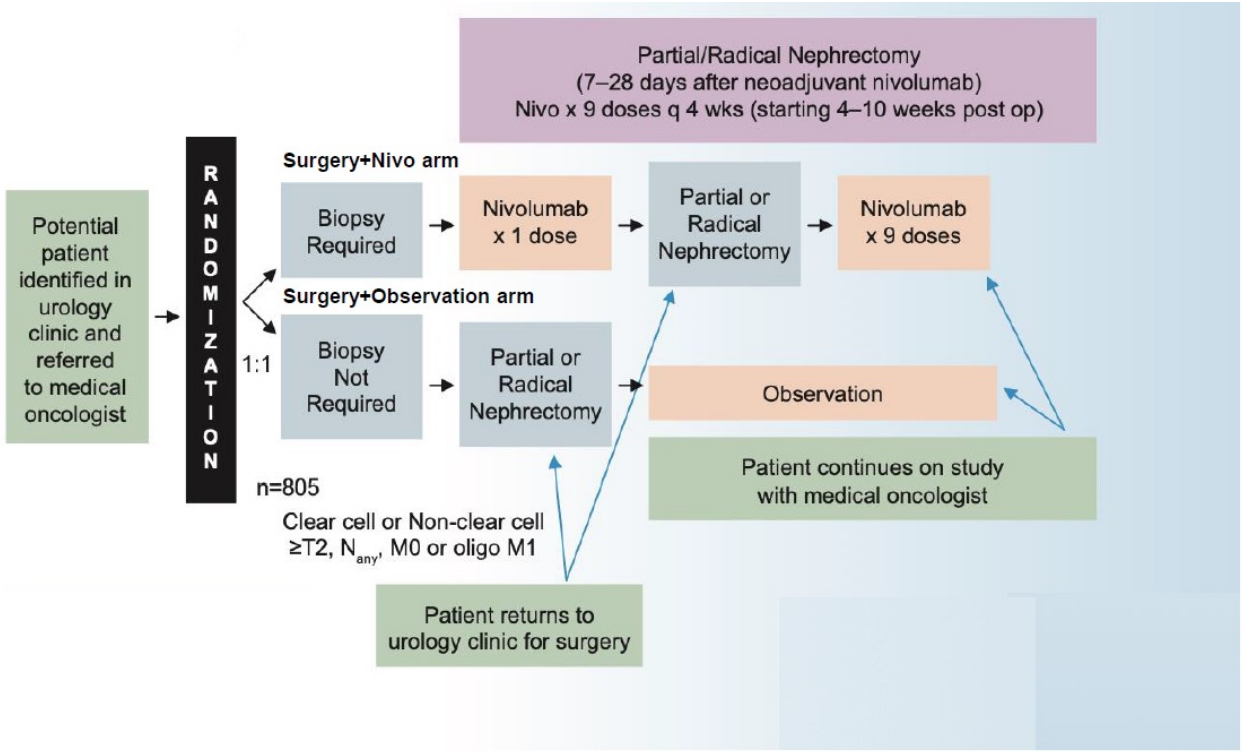

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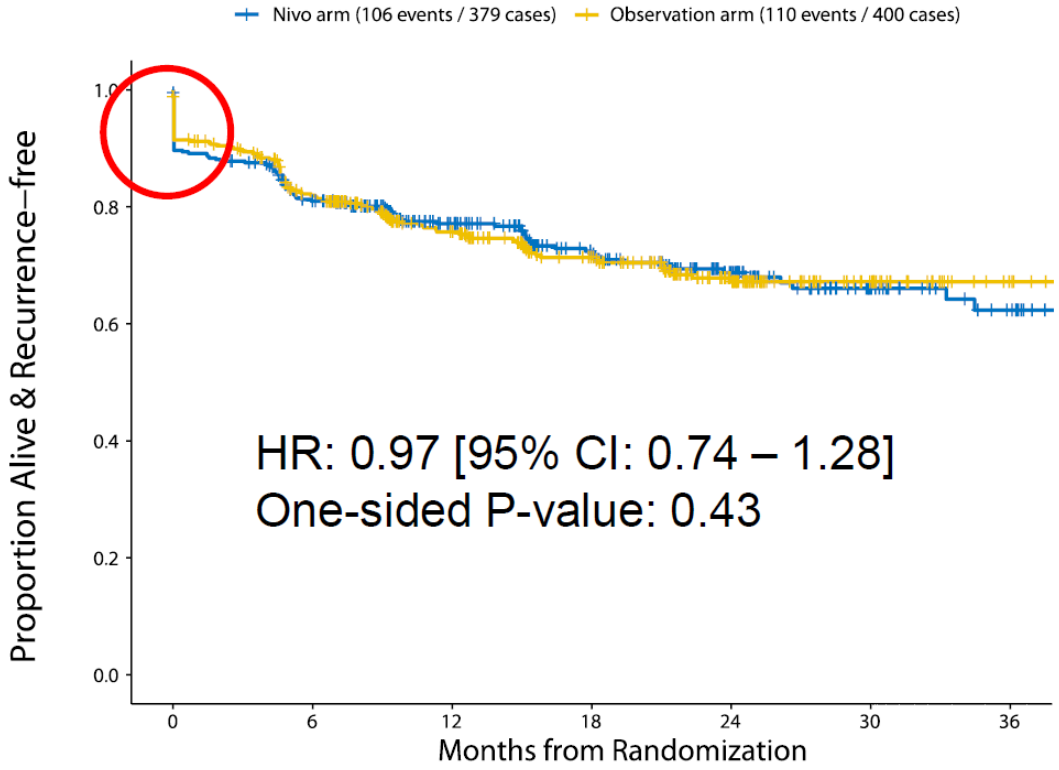
ECOG-ACRIN EA8143: PROSPER



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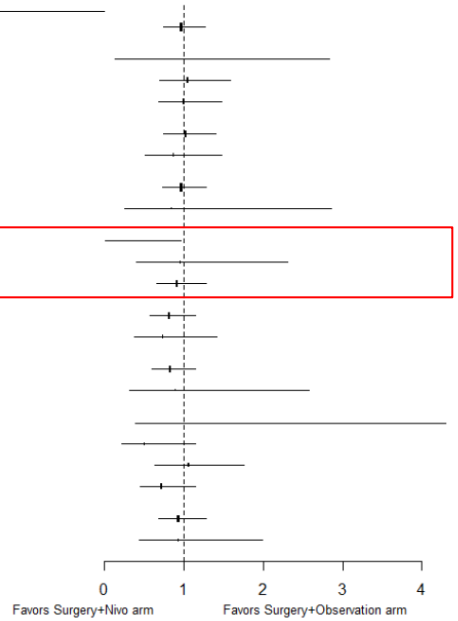
ECOG-ACRIN EA8143: PROSPER

	Surgery+Nivo arm n = 404	Surgery+Observation arm n = 415	Total n = 819
	N (%)	N (%)	N (%)
Pathologic T-stage			
T1	35 (10)	42 (11)	77 (10)
T2	83 (24)	81 (21)	164 (22)
T3 or T4	233 (66)	261 (68)	494 (67)
Pathologic N-stage			
Nx/N0	316 (90)	355 (92)	671 (91)
N1	36 (10)	30 (8)	66 (9)
Pathologic M-stage			
Mx/M0	340 (97)	368 (96)	708 (96)
M1	12 (3)	16 (4)	28 (4)
Surgery Type			
Radical	344 (96)	375 (95)	719 (95)
Surgery Histology			
Clear cell	278 (78)	306 (77)	584 (77)
Papillary	27 (8)	20 (5)	47 (6)
Chromophobe	24 (7)	21 (5)	45 (6)
Sarcomatoid features			
Yes	30 (8)	49 (12)	79 (11)
Fuhrman grade			
1	14 (4)	10 (3)	24 (4)
2	89 (28)	96 (27)	185 (28)
3	136 (42)	146 (41)	282 (42)
4	81 (25)	100 (28)	181 (27)

Sub-group	N	HR	95% CI
All RCC Patients	779	0.97	(0.74, 1.27)
cT1	25	0.61	(0.13, 2.83)
cT2	398	1.05	(0.69, 1.59)
cT3 or cT4	394	1.00	(0.68, 1.47)
cNx or cN0	697	1.02	(0.74, 1.40)
cN1	121	0.87	(0.51, 1.47)
cMx or cM0	790	0.97	(0.73, 1.28)
cM1	27	0.85	(0.25, 2.86)
pTx or pT1	79	0.12	(0.01, 0.96)
pT2	164	0.96	(0.40, 2.31)
pT3 or pT4	494	0.91	(0.65, 1.28)
pNx or pN0	671	0.81	(0.57, 1.14)
pN1	66	0.73	(0.37, 1.41)
pMx or pM0	708	0.83	(0.60, 1.14)
pM1	28	0.89	(0.31, 2.57)
Fuhrman Grade 1	24	3.37	(0.38, 30.18)
Fuhrman Grade 2	185	0.50	(0.21, 1.15)
Fuhrman Grade 3	282	1.06	(0.63, 1.76)
Fuhrman Grade 4	181	0.72	(0.45, 1.14)
Clear-cell	625	0.93	(0.68, 1.28)
Non-clear cell	128	0.93	(0.44, 1.99)



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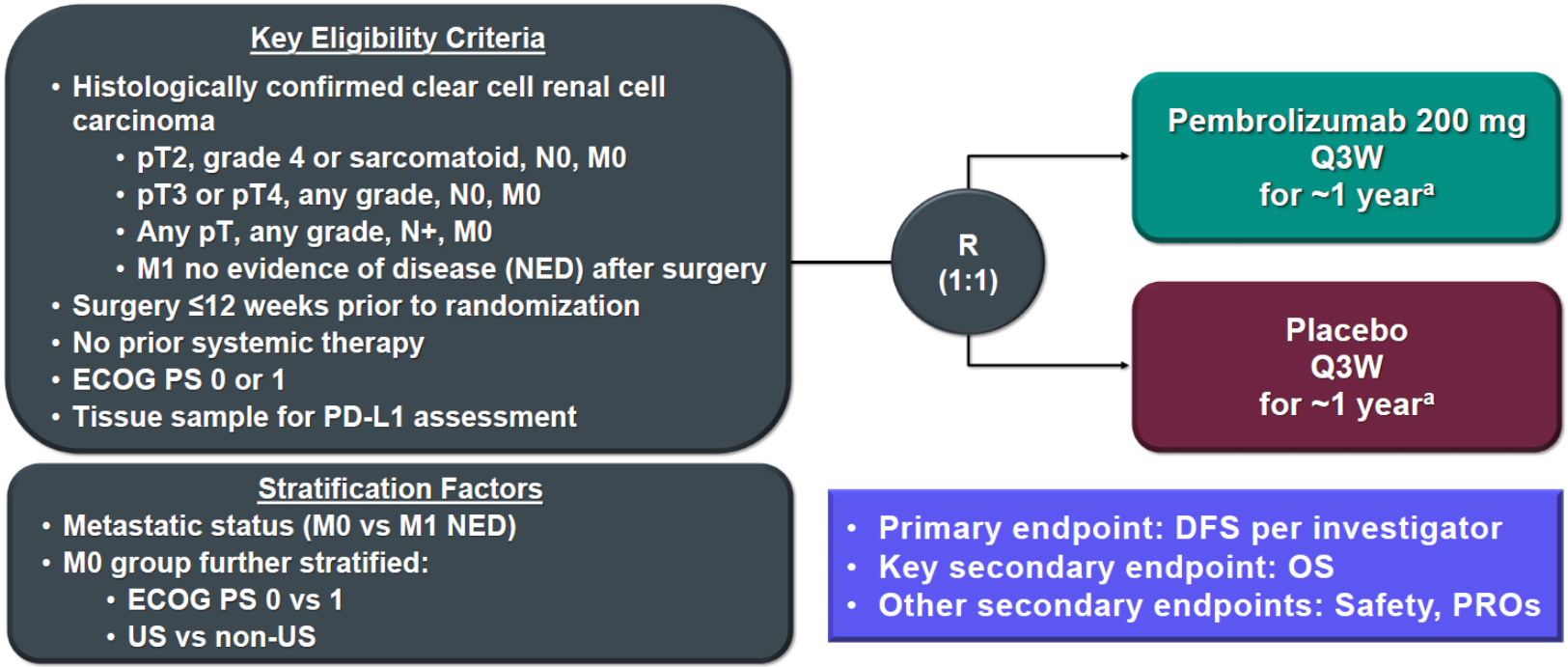
KEYNOTE-564 (NCT03142334)



Choueiri *et al* NEJM 2021

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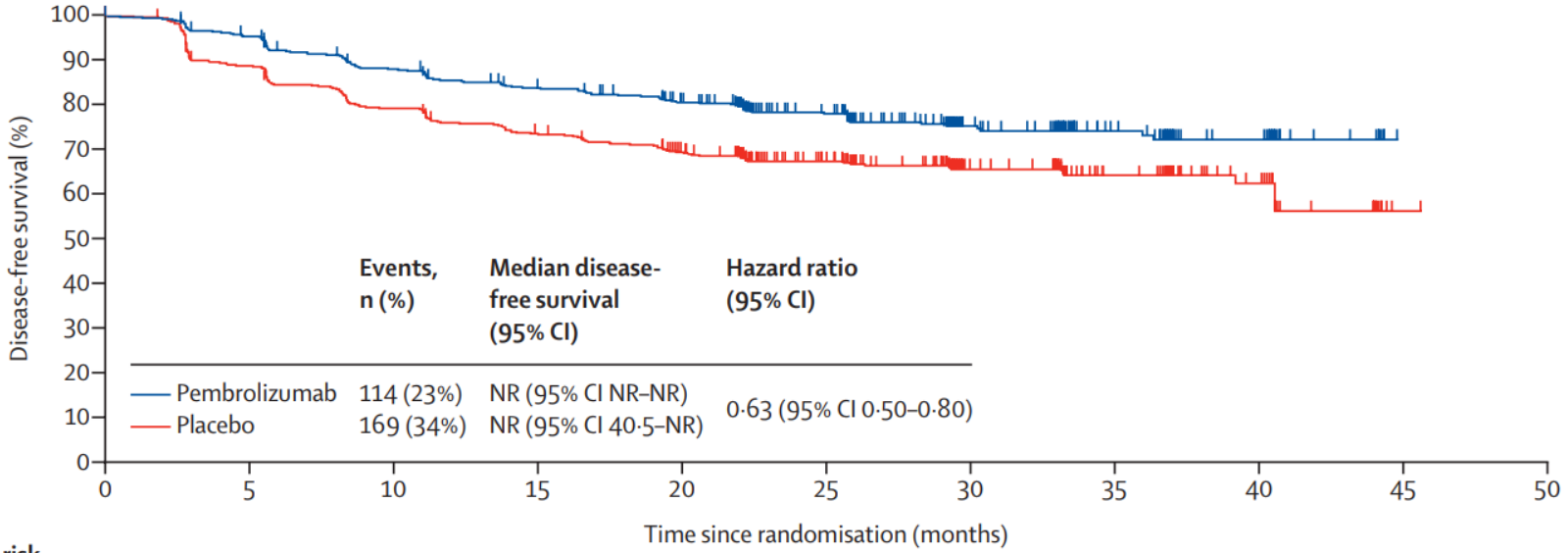

Number at risk (number censored)											
Pembrolizumab	496 (0)	458 (16)	416 (23)	398 (30)	361 (43)	255 (139)	135 (251)	77 (307)	37 (345)	0 (382)	0 (382)
Placebo	498 (0)	437 (6)	389 (7)	356 (11)	325 (23)	230 (109)	125 (209)	74 (258)	33 (298)	1 (328)	0 (329)

Powles *et al* Lancet Oncol 2022

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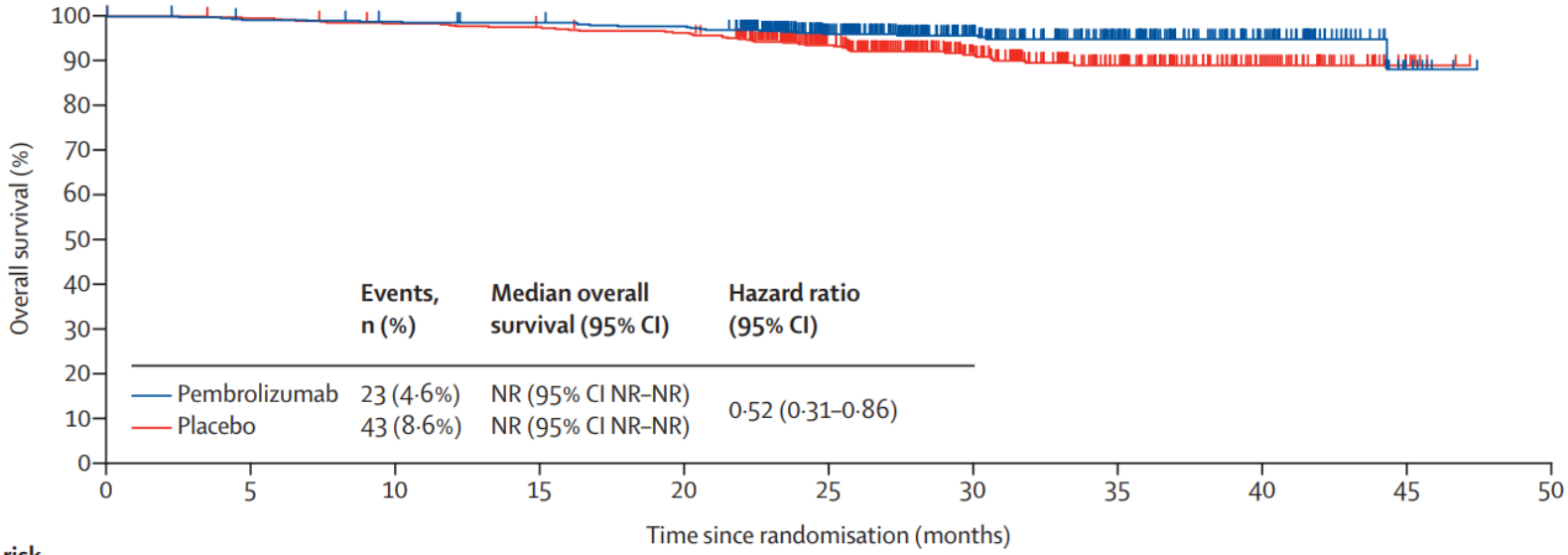

Number at risk (number censored)											
Pembrolizumab	496 (3)	489 (3)	485 (5)	482 (7)	477 (8)	360 (117)	231 (245)	146 (328)	63 (411)	8 (465)	0 (473)
Placebo	498 (0)	494 (2)	486 (4)	481 (5)	474 (6)	352 (115)	219 (241)	138 (317)	61 (394)	9 (446)	0 (455)

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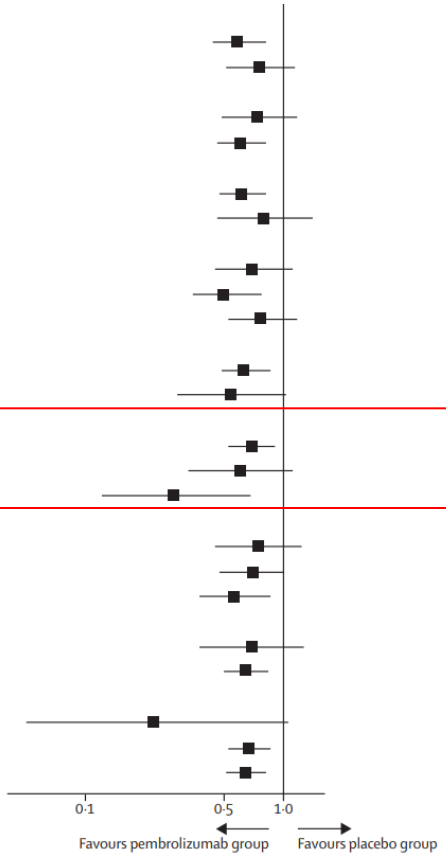
KEYNOTE-564 (NCT03142334)

Age, years			
<65	71/338	109/326	0·58 (0·43–0·79)
≥65	43/158	60/172	0·75 (0·51–1·11)
Sex			
Female	38/149	46/139	0·73 (0·48–1·13)
Male	76/347	123/359	0·60 (0·45–0·80)
ECOG performance score			
0	91/421	141/426	0·61 (0·47–0·79)
1	23/75	28/72	0·79 (0·45–1·37)
Region			
North America	32/133	44/125	0·69 (0·44–1·09)
EU	38/188	68/187	0·50 (0·34–0·75)
Rest of the world	44/175	57/186	0·77 (0·52–1·14)
Sarcomatoid features			
Absent	88/414	133/415	0·63 (0·48–0·83)
Present	16/52	29/59	0·54 (0·29–1·00)
Disease risk category			
M0 intermediate-high	87/422	127/433	0·68 (0·52–0·89)
M0 high	20/40	23/36	0·60 (0·33–1·10)
M1 no evidence of disease	7/29	19/29	0·28 (0·12–0·66)
Tumour grade			
2	27/153	36/150	0·73 (0·44–1·20)
3	49/219	68/213	0·68 (0·47–0·98)
4	36/103	63/119	0·55 (0·37–0·83)
PD-L1 status			
CPS <1	19/124	25/113	0·68 (0·37–1·24)
CPS ≥1	93/365	143/383	0·63 (0·49–0·82)
Type of nephrectomy			
Partial	2/37	8/38	0·22 (0·05–1·04)
Radical	112/459	161/460	0·66 (0·52–0·85)
Overall	**114/496**	**169/498**	**0·63 (0·50–0·80)**



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The Bottom Line …

KEYNOTE-564

Key Eligibility Criteria
- Histologically confirmed clear cell renal cell carcinoma
  - pT2, grade 4 or sarcomatoid, N0, M0
  - pT3 or pT4, any grade, N0, M0
  - Any pT, any grade, N+, M0
  - M1 no evidence of disease (NED) after surgery
- Surgery ≤12 weeks prior to randomization
- No prior systemic therapy
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment

Stratification Factors
- Metastatic status (M0 vs M1 NED)
- M0 group further stratified:
  - ECOG PS 0 vs 1
  - US vs non-US

R (1:1)

- Pembrolizumab 200 mg Q3W for ~1 year[a]
- Placebo Q3W for ~1 year[a]

- Primary endpoint: DFS per investigator
- Key secondary endpoint: OS
- Other secondary endpoints: Safety, PROs

Immotion010

Key eligibility criteria
- Resected intermediate- to high-risk[a] RCC
  - T2 Grade 4
  - T3a Grade 3/4
  - T3b/c or T4 any Grade
  - TXN+ any Grade
  - M1 NED[b]
- Clear cell and/or sarcomatoid component

R 1:1 N=778

- Atezolizumab 1200 mg IV q3w for 16 cycles or 1 year[c]
- Placebo IV q3w for 16 cycles or 1 year[c]

Stratification factors
- **Disease stage** (T2/T3a vs T3b/c/T4/N+ vs M1 NED)
- **PD-L1 expression on IC[d]** (IC0 [<1%] vs IC1/2/3 [≥1%])
- **Region** (North America[e] vs rest of world)

Primary endpoint
- Investigator-assessed DFS in ITT population

Key secondary endpoints
- OS in the ITT population
- Investigator-assessed DFS in the IC1/2/3 population
- IRF-assessed DFS in the ITT and IC1/2/3 populations
- IRF-assessed EFS in the ITT population
- Safety

CheckMate 914

N = 816

Key inclusion criteria[1]
- Radical or partial nephrectomy with negative surgical margins
- Predominant clear cell histology, including sarcomatoid features
- Pathologic TNM staging:
  - pT2a, G3 or G4, N0 M0
  - pT2b, G any, N0 M0
  - pT3, G any, N0 M0
  - pT4, G any, N0 M0
  - pT any, G any, N1 M0
- No clinical/radiological evidence of residual disease or distant metastases after nephrectomy, confirmed by BICR
- ECOG performance status of 0-1

Stratification factors:
- Pathologic TNM staging[a]
- Type of nephrectomy

R 1:1

Randomization > 4 weeks but ≤ 12 weeks after surgery

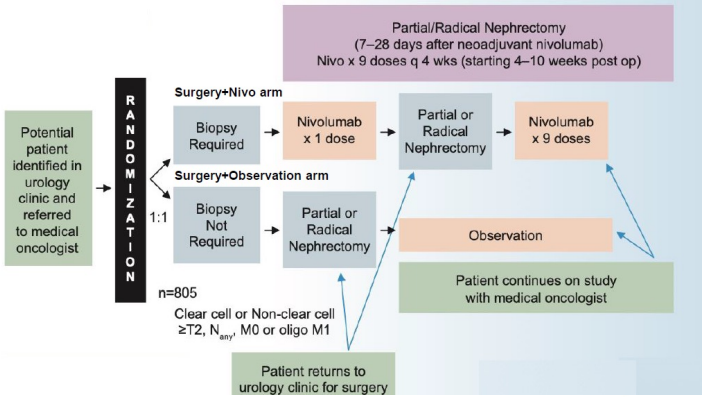
Expected treatment duration of 24 weeks[b]

- **NIVO** 240 mg IV Q2W (× 12 doses) + **IPI** 1 mg/kg IV Q6W (× 4 doses) N = 405
- **Placebo** IV Q2W (× 12 doses) + **Placebo** IV Q6W (× 4 doses) N = 411

Primary endpoint: DFS by BICR

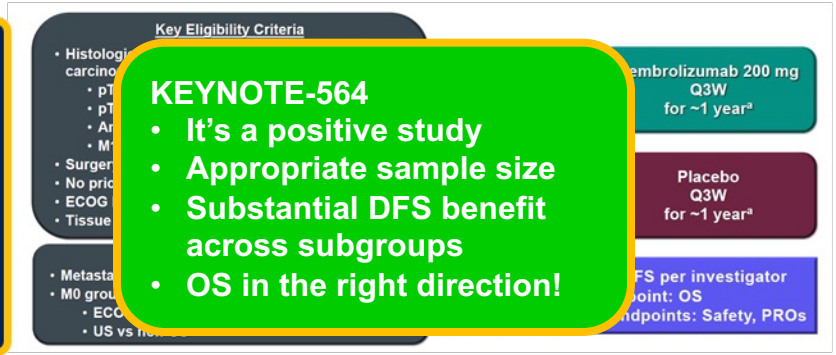
Secondary endpoints: OS and safety

ECOG PROSPER



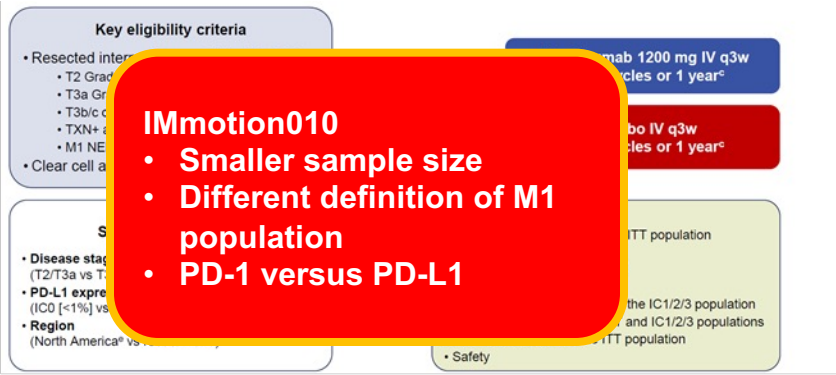
The Bottom Line …

KEYNOTE-564



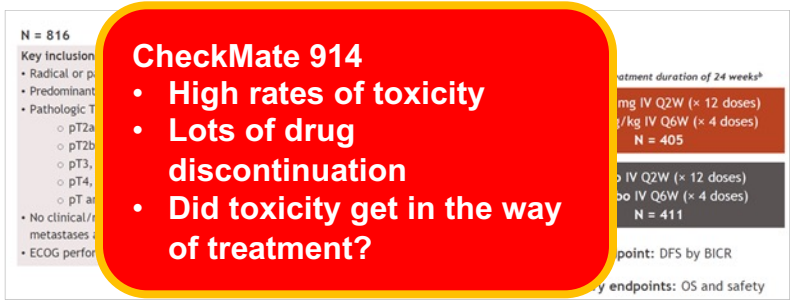
KEYNOTE-564
- It's a positive study
- Appropriate sample size
- Substantial DFS benefit across subgroups
- OS in the right direction!

Immotion010



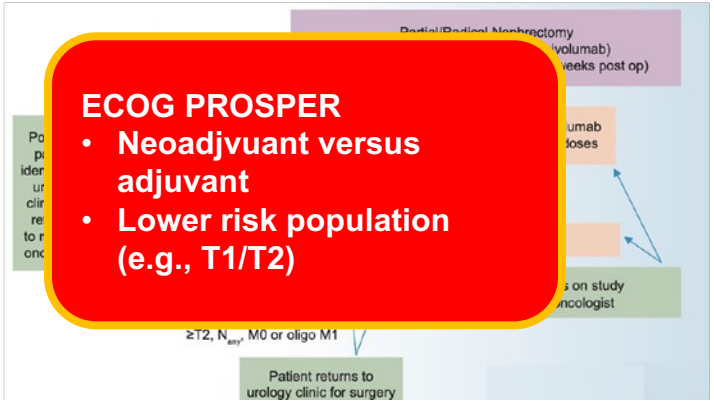
IMmotion010
- Smaller sample size
- Different definition of M1 population
- PD-1 versus PD-L1

CheckMate 914



CheckMate 914
- High rates of toxicity
- Lots of drug discontinuation
- Did toxicity get in the way of treatment?

ECOG PROSPER



ECOG PROSPER
- Neoadjvuant versus adjuvant
- Lower risk population (e.g., T1/T2)

Practice Changing Front-Line Trials in mRCC

ESMO 2017: Nivolumab/Ipilimumab vs Sunitinib

ASCO GU 2019: Axitinib/Pembrolizumab vs Sunitinib

ESMO 2020: Cabozantinib/Nivolumab vs Sunitinib

ASCO GU 2021: Lenvatinib/Pembrolizumab vs L/E vs Sunitinib

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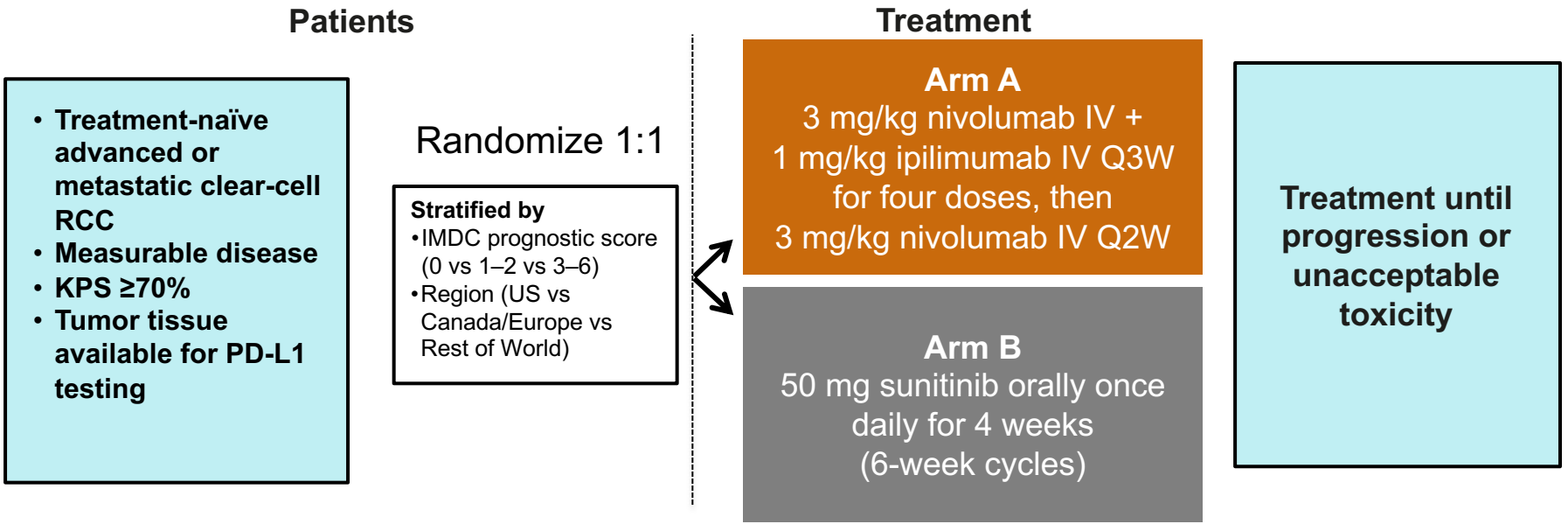
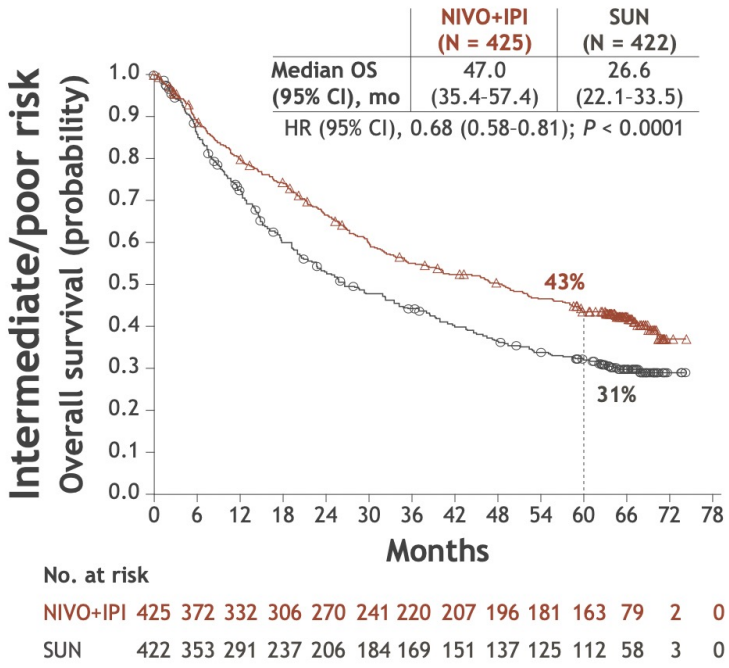
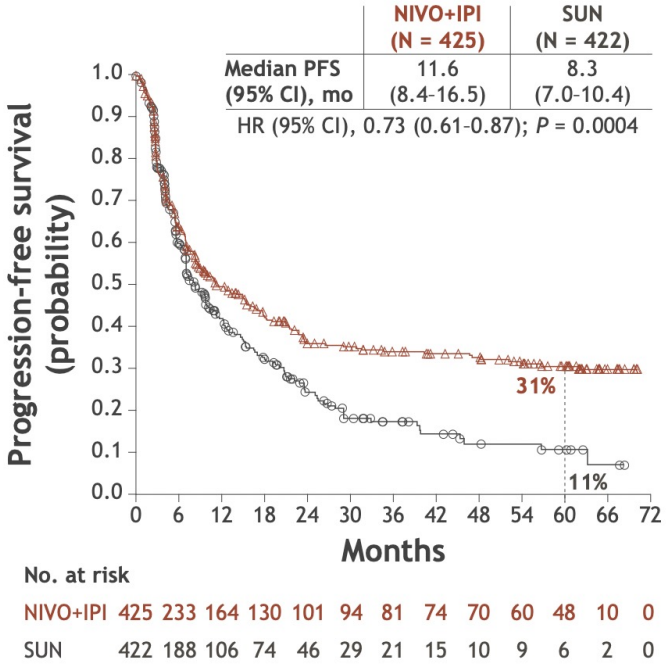
CheckMate 214: See Talk from Dr. Hammers



Escudier et al ESMO 2017

CheckMate 214: 5-year Update





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CheckMate 214: 5-year Update

Response assessment	ITT		I/P risk		FAV risk	
	NIVO+IPI (N = 550)	SUN (N = 546)	NIVO+IPI (N = 425)	SUN (N = 422)	NIVO+IPI (N = 125)	SUN (N = 124)
Confirmed ORR, % (95% CI)	39.3 (35.2-43.5)	32.4 (28.5-36.5)	42.1 (37.4-47.0)	26.8 (22.6-31.3)	29.6 (21.8-38.4)	51.6 (42.5-60.7)
P value	0.0055		< 0.0001		0.0002	
BOR, n (%)						
CR	64 (11.6)	17 (3.1)	48 (11.3)	9 (2.1)	16 (12.8)	8 (6.5)
PR	152 (27.6)	160 (29.3)	131 (30.8)	104 (24.6)	21 (16.8)	56 (45.2)
SD	198 (36.0)	230 (42.1)	131 (30.8)	187 (44.3)	67 (53.6)	43 (34.7)
PD	97 (17.6)	77 (14.1)	82 (19.3)	71 (16.8)	15 (12.0)	6 (4.8)
UTD	38 (6.9)	57 (10.4)	32 (7.5)	48 (11.4)	6 (4.8)	9 (7.3)
NR	1 (0.2)	5 (0.9)	1 (0.2)	3 (0.7)	0	2 (1.6)
Ongoing response, n (%)	n = 216 136 (63.0)	n = 177 89 (50.3)	n = 179 114 (63.7)	n = 113 56 (49.6)	n = 37 22 (59.5)	n = 64 33 (51.6)
Ongoing CR, n (%)	n = 64 54 (84.4)	n = 17 15 (88.2)	n = 48 41 (85.4)	n = 9 8 (88.9)	n = 16 13 (81.3)	n = 8 7 (87.5)

CI, confidence interval; NR, not reported; PD, progressive disease; PR, partial response; SD, stable disease; UTD, unable to determine.

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Practice Changing Front-Line Trials in mRCC

ESMO 2017: Nivolumab/Ipilimumab vs Sunitinib

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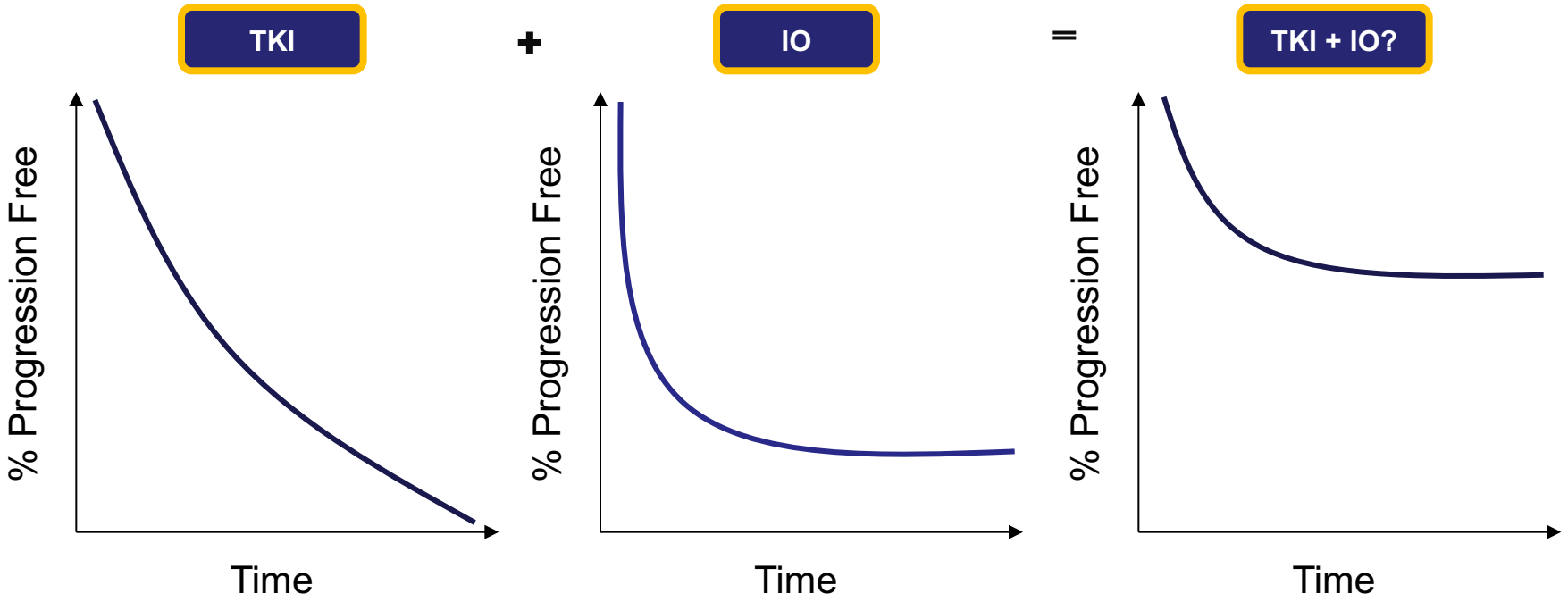
Objective of combination therapy



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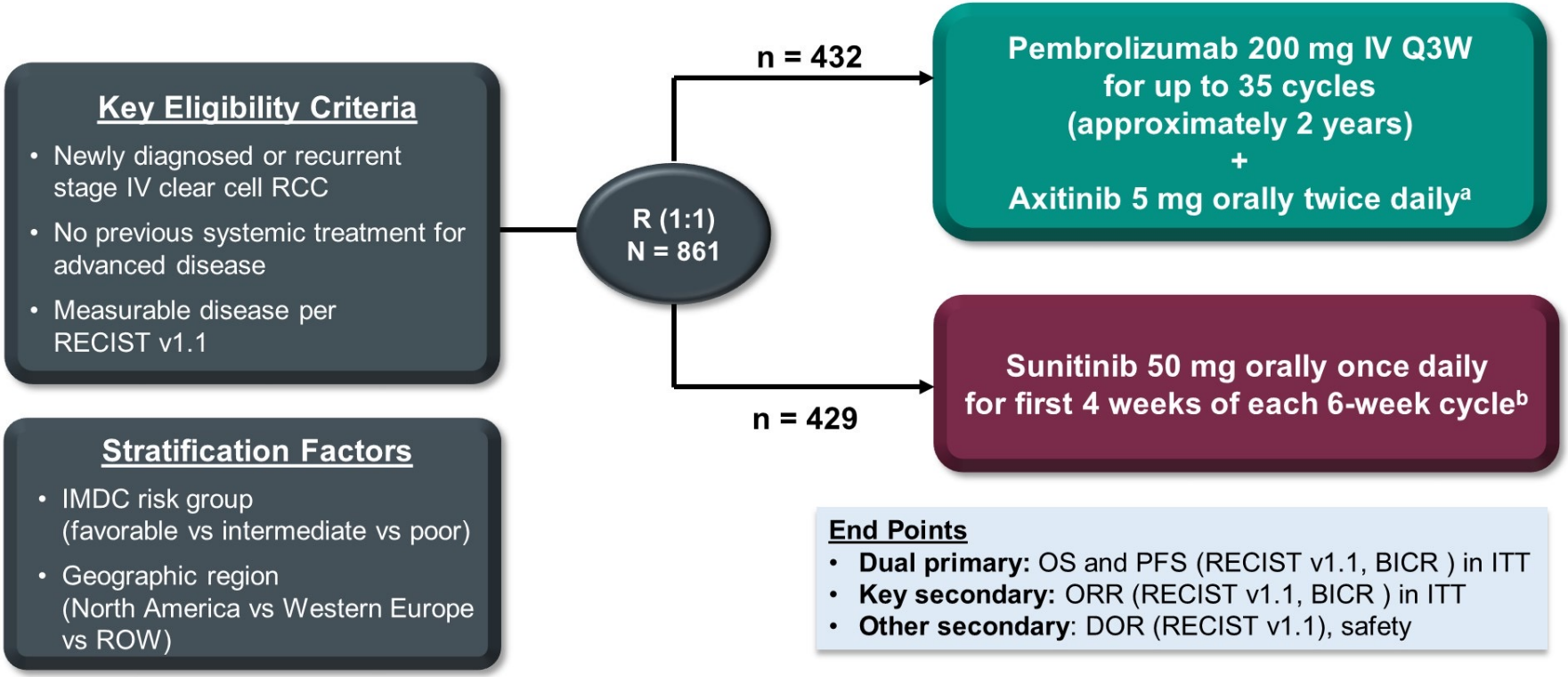
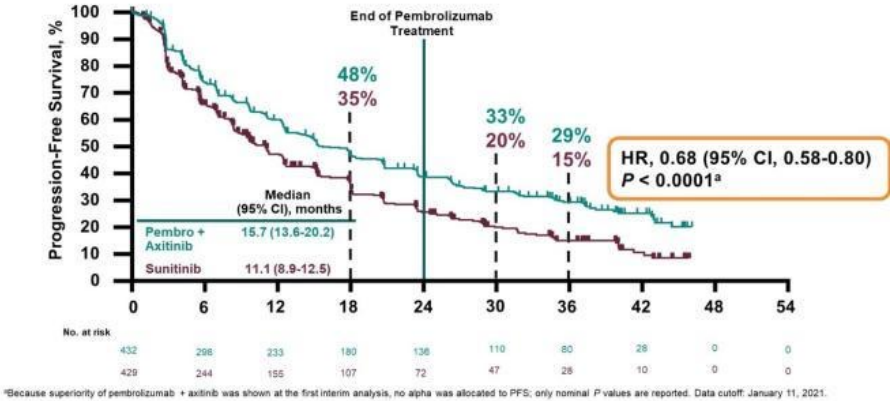
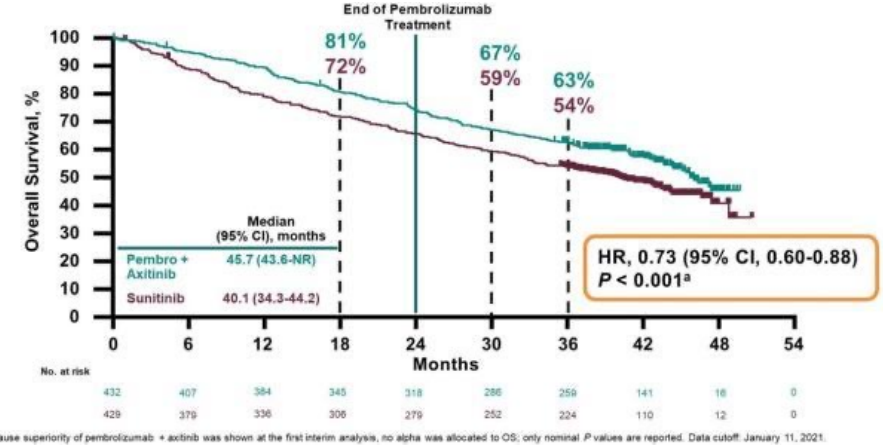
KEYNOTE-426 Study Design



[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity. [b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 weeks of each 6-week cycle to manage toxicity. Data cutoff: January 11, 2021.

KEYNOTE-436: PFS and OS 42-month Follow-up





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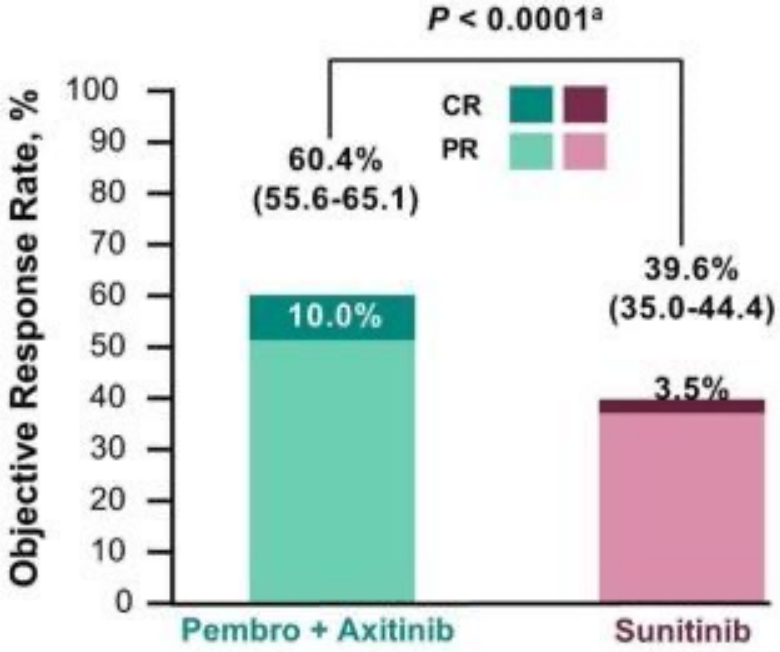
KEYNOTE-436: PFS and OS 42-month Follow-up



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

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Practice Changing Front-Line Trials in mRCC

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ASCO GU 2021: Lenvatinib/Pembrolizumab vs L/E vs Sunitinib

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CheckMate 9ER: Study design

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

N = 651

Key inclusion criteria[1,2]
- Previously untreated advanced or metastatic RCC
- Clear cell component
- Any IMDC risk group

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]

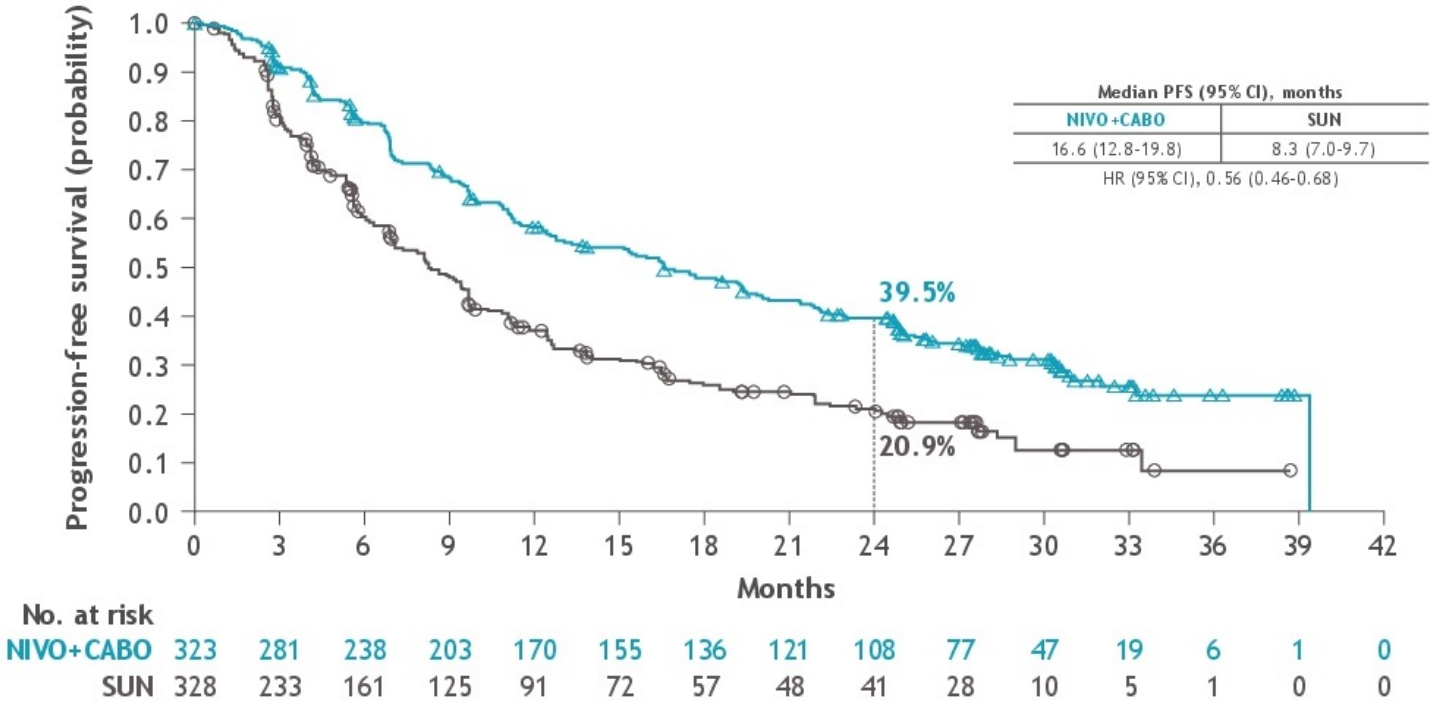
Median study follow-up, 18.1 months (range, 10.6–30.6 months)

Primary endpoint: PFS

Secondary endpoints: OS, ORR, and safety

[a]Defined as the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry 28-8 pharmDx assay.
[b]NIVO dosing may not exceed a total of 2 years (from cycle 1); CABO and SUN treatment may continue beyond 2 years in the absence of progression or unacceptable toxicity. Patients may be treated beyond progression.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IV, intravenously; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; PO, orally; Q2W, every 2 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.
1. Clinicaltrials.gov/ct2/show/NCT03141177. Accessed June 8, 2020; 2. Choueiri TK et al. Poster presented at the American Society of Clinical Oncology Annual Meeting 2018. TPS4598.

CheckMate 9ER: PFS and OS 32.9 month follow-up



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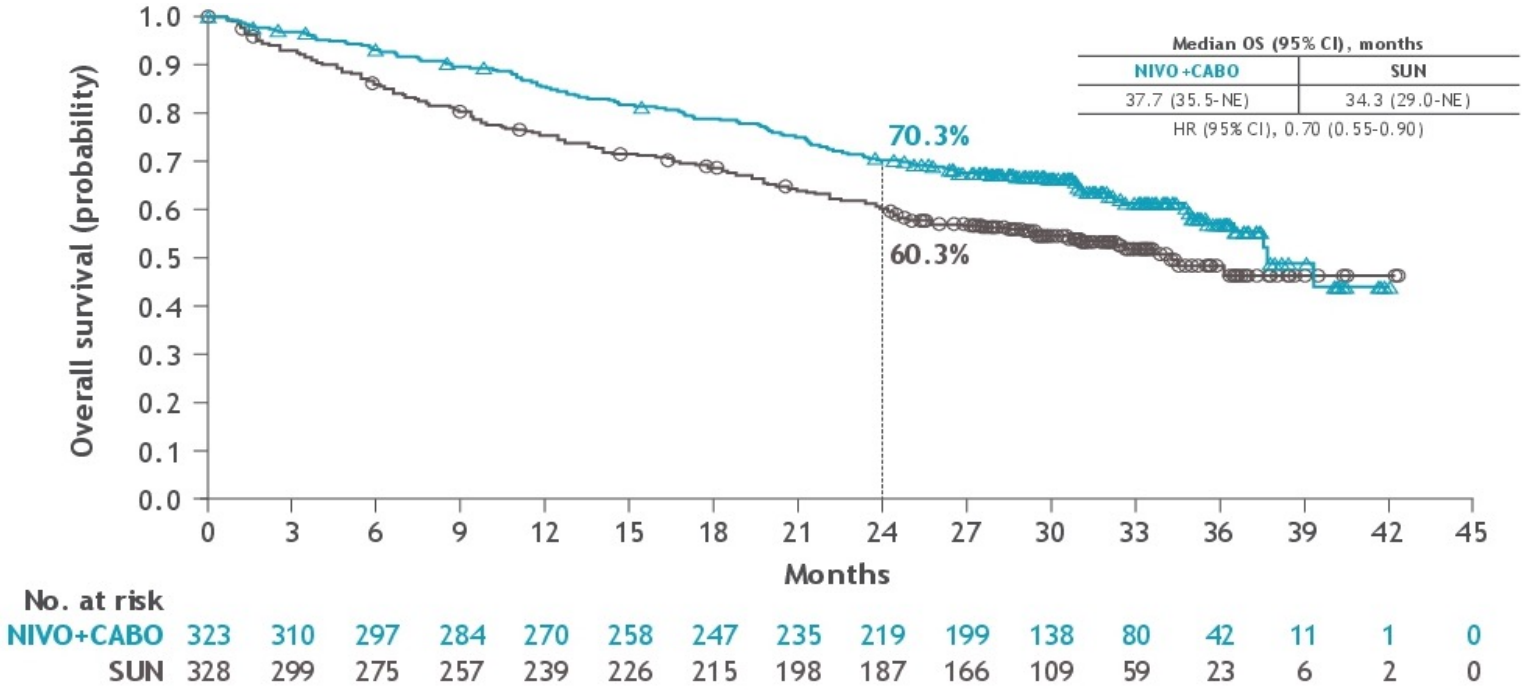
CheckMate 9ER: PFS and OS 32.9 month follow-up



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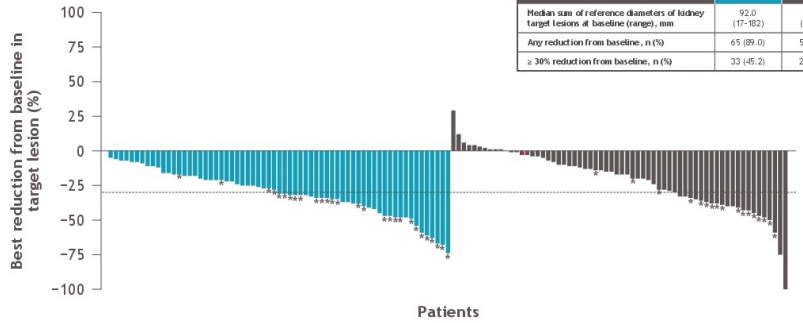
CheckMate 9ER: PFS and OS 32.9 month follow-up

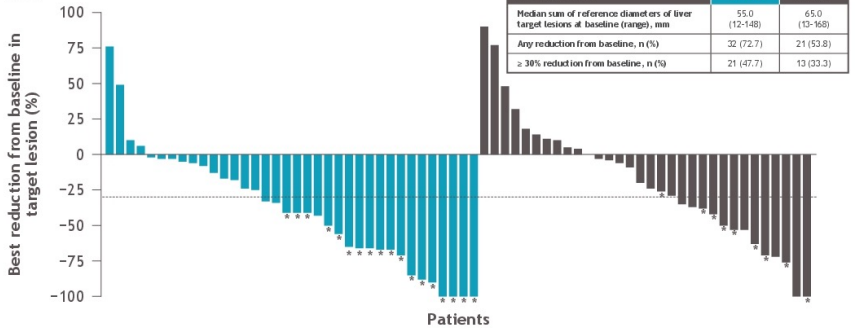
Kidney

Kidney target lesion[a]	NIVO+CABO (n = 73)	SUN (n = 74)
Median sum of reference diameters of kidney target lesions at baseline (range), mm	92.0 (17-182)	93.0 (15-265)
Any reduction from baseline, n (%)	65 (89.0)	53 (71.6)
≥ 30% reduction from baseline, n (%)	33 (45.2)	22 (29.7)



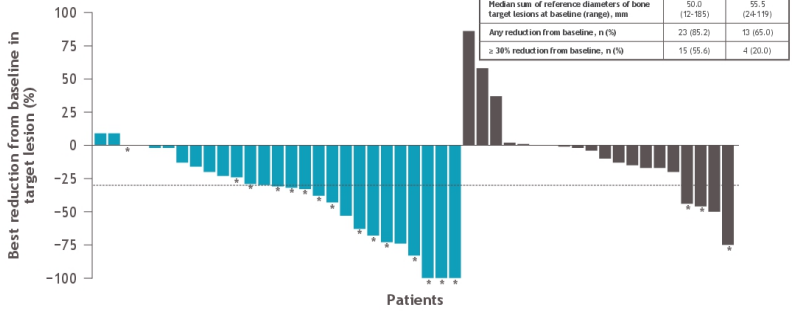
Liver

Liver target lesion[a]	NIVO+CABO (n = 44)	SUN (n = 39)
Median sum of reference diameters of liver target lesions at baseline (range), mm	55.0 (12-148)	65.0 (13-168)
Any reduction from baseline, n (%)	32 (72.7)	21 (53.8)
≥ 30% reduction from baseline, n (%)	21 (47.7)	13 (33.3)



Bone

Bone target lesion[b]	NIVO+CABO (n = 27)	SUN (n = 20)
Median sum of reference diameters of bone target lesions at baseline (range), mm	50.0 (12-185)	55.5 (24-119)
Any reduction from baseline, n (%)	23 (85.2)	13 (65.0)
≥ 30% reduction from baseline, n (%)	15 (55.6)	4 (20.0)



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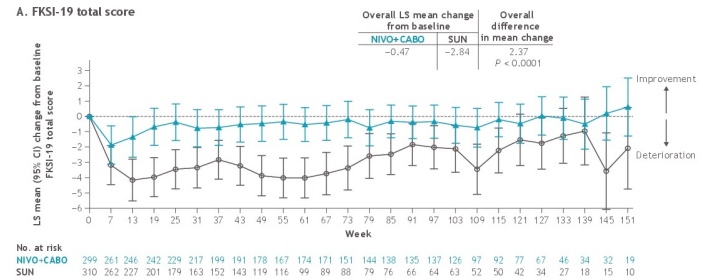
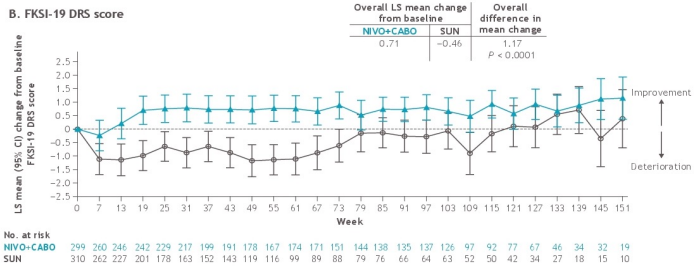
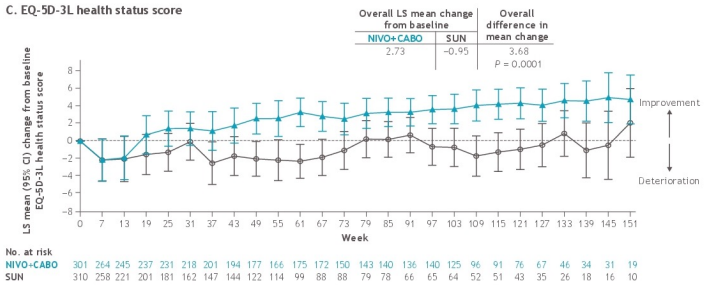
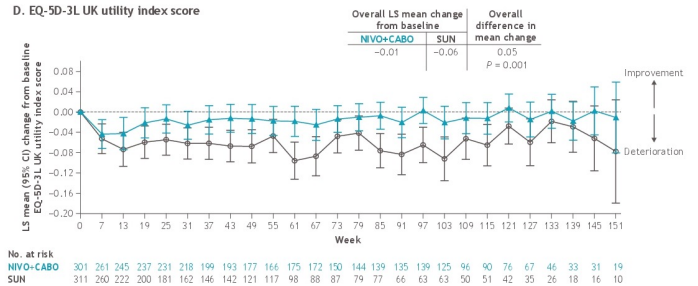
CheckMate 9ER: PFS and OS 32.9 month follow-up









Powles ASCO GU 22

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Practice Changing Front-Line Trials in mRCC

ESMO 2017: Nivolumab/Ipilimumab vs Sunitinib

ASCO GU 2019: Axitinib/Pembrolizumab vs Sunitinib

ESMO 2020: Cabozantinib/Nivolumab vs Sunitinib

ASCO GU 2021: Lenvatinib/Pembrolizumab vs L/E vs Sunitinib

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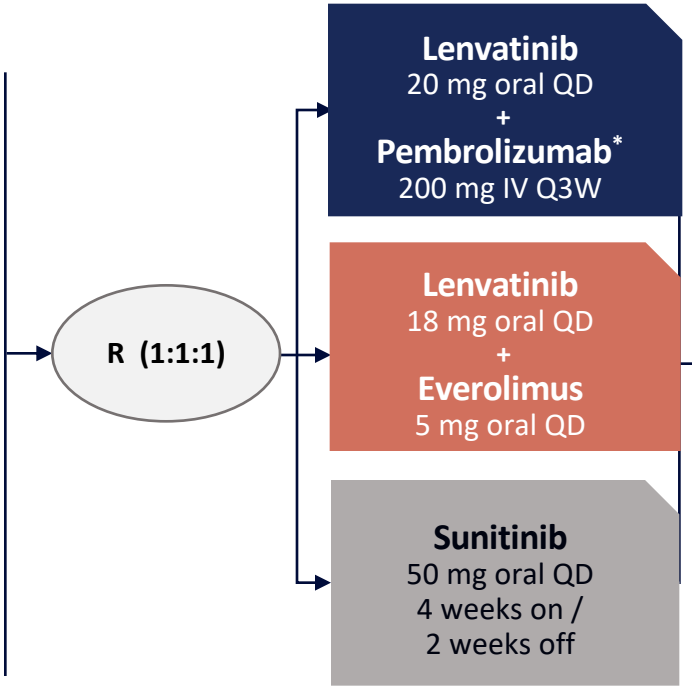
Study Design

Key eligibility criteria

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

Stratification factors

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



Primary endpoint

- PFS by IRC per RECIST v1.1

Secondary endpoints

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

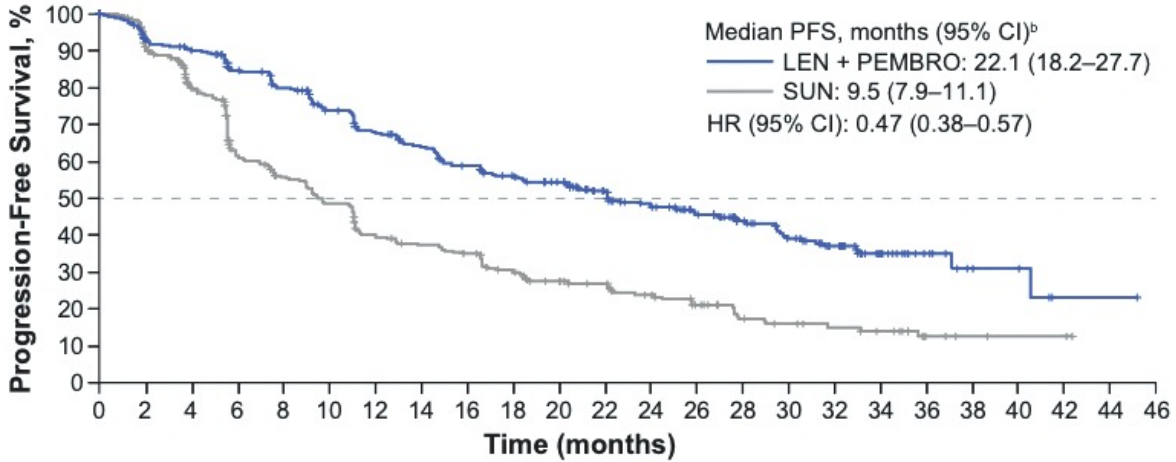
Key exploratory endpoints

- DOR
- Biomarkers

*Patients could receive a maximum of 35 pembrolizumab treatments.

DOR, duration of response; HRQoL, Health-related quality of life; IRC, Independent Review Committee; MKSCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate; OS, overall survival; R, randomization.

CLEAR: OS and PFS 33 month follow-up



Number of patients at risk:

LEN + PEMBRO	355	317	304	277	258	230	207	191	173	158	146	122	104	90	71	57	44	24	12	6	5	1	1	0
SUN	357	281	234	171	149	130	103	95	88	72	60	54	44	34	24	20	17	14	5	3	2	2	0	

[a]Data cutoff occurred on March 31, 2021; [b]at the earlier (August 28, 2020) data cutoff, the median PFS by investigator per RECIST v1.1 was 22.1 months (95% CI 17.1–26.9) in the LEN + PEMBRO arm and 9.5 months (95% CI 7.9–11.1) in the SUN arm (HR 0.47; 95% CI 0.38–0.58).
CI, confidence interval; HR, hazard ratio; LEN, lenvatinib; PEMBRO, pembrolizumab; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SUN, sunitinib.

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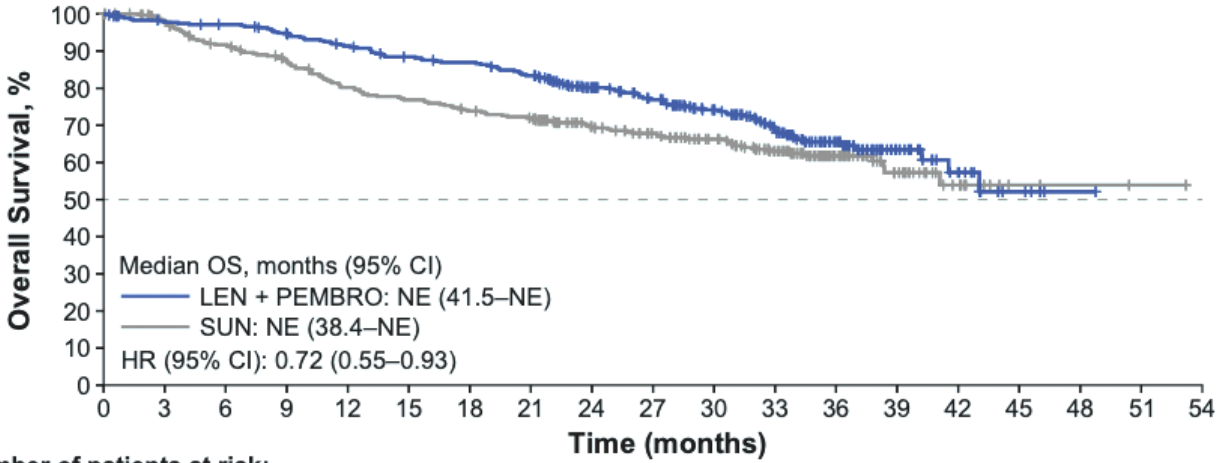
CLEAR: OS and PFS 33 month follow-up



Number of patients at risk:

LEN + PEMBRO	355	342	338	327	313	300	294	280	232	207	174	133	75	31	15	5	1	0
SUN	357	332	307	289	264	253	242	234	195	177	153	116	66	34	14	3	2	1	0

[a]Data cutoff occurred on March 31, 2021.

CI, confidence interval; HR, hazard ratio; LEN, lenvatinib; NE, not estimable; OS, overall survival; PEMBRO, pembrolizumab; SUN, sunitinib.

Choueiri et al IKCS 2021

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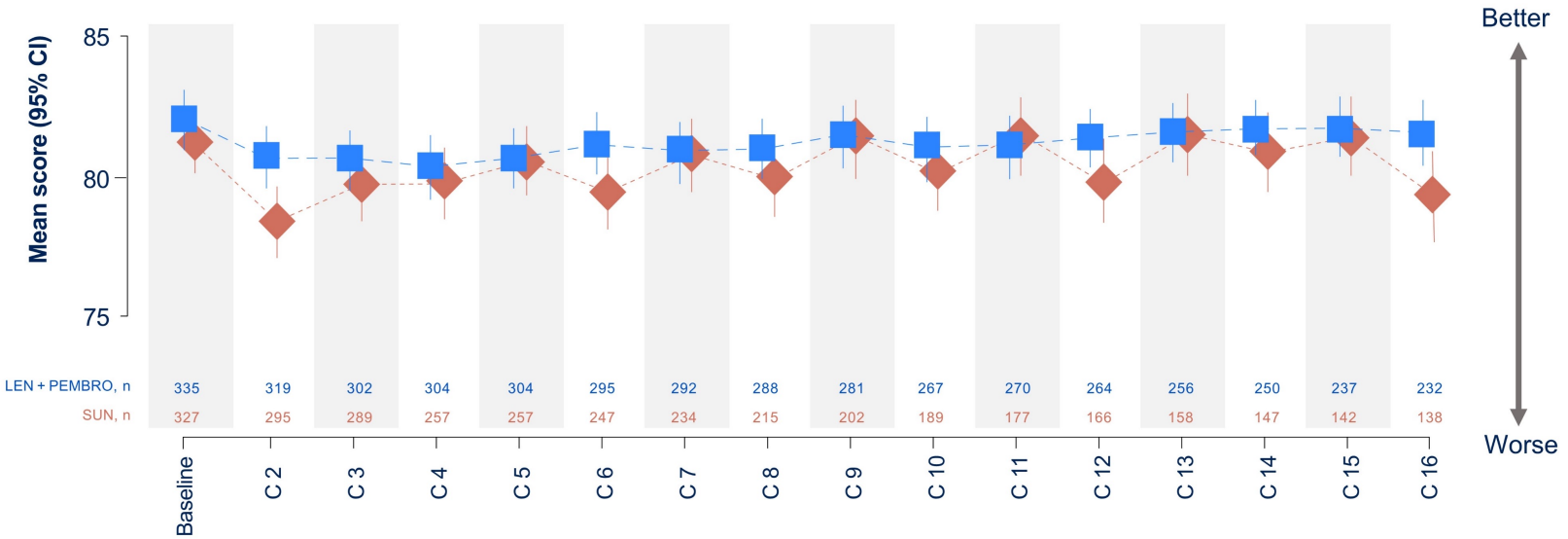
Mean EORTC QLQ-C30 Physical Functioning Score: LEN + PEMBRO vs SUN



Scores for this scale range from 0 to 100. Mean follow-up time for HRQoL during treatment was 46 weeks (cycle 15).
C, cycle.

Algorithm incorporating emerging first-line options

<table>
<tr><th>Treatment</th><th colspan="2">First-Line</th><th>Second-Line</th></tr>
<tr><td rowspan="2">Good risk</td><td colspan="2">Cabozantinib/Nivolumab</td><td rowspan="2">Lenvatinib/Everolimus</td></tr>
<tr><td colspan="2">Cabozantinib*</td></tr>
<tr><td rowspan="3">Intermediate/Poor-risk</td><td>Considering Nephrectomy</td><td rowspan="2">Nivolumab/Ipilimumab</td><td rowspan="3">Tivozanib*</td></tr>
<tr><td>Not Considering Nephrectomy</td><td>Cabozantinib/Nivolumab</td></tr>
<tr><td colspan="2">Cabozantinib*</td></tr>
</table>

* Special circumstances, refer to discussion

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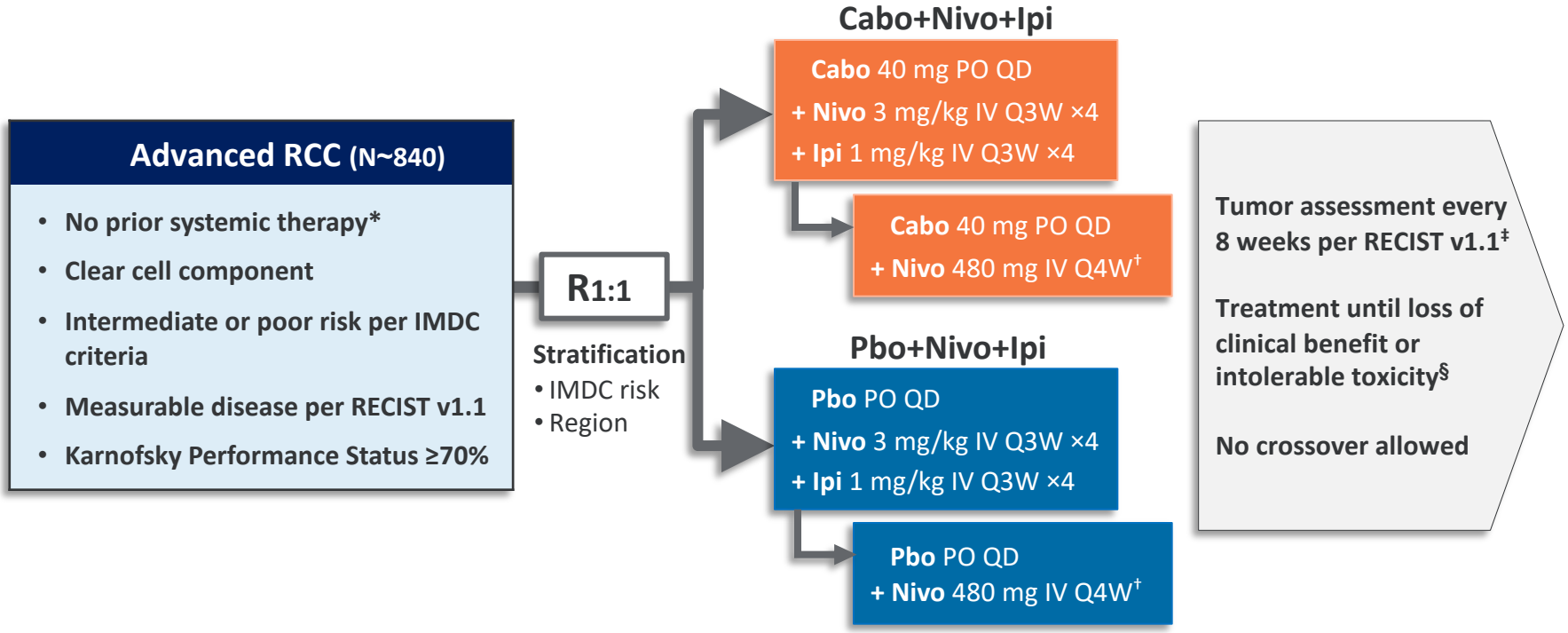
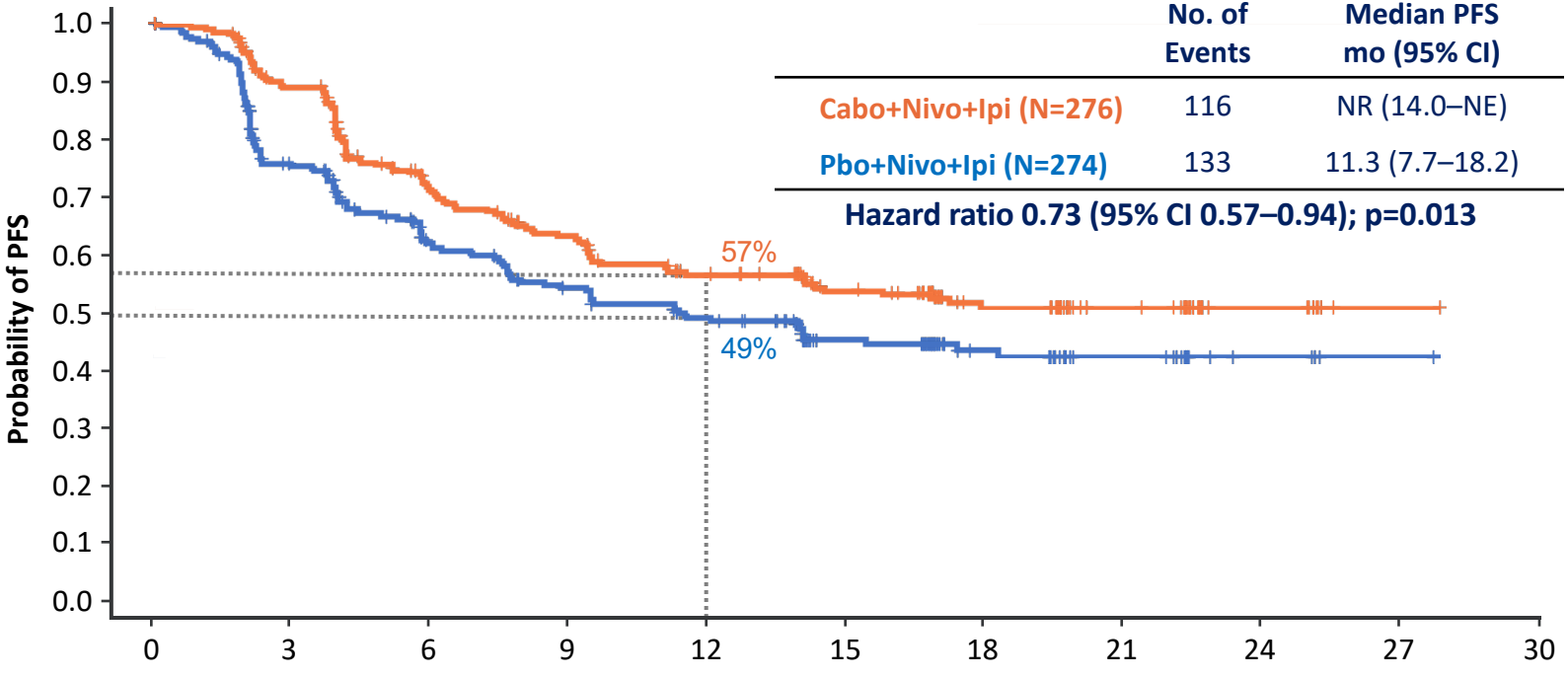
COSMIC-313 Study Design



*One prior systemic adjuvant therapy allowed for completely resected RCC and if recurrence occurred ≥6 months after the last dose of adjuvant therapy; adjuvant PD-1 or PD-L1 inhibitor in combination with a CTLA-4 inhibitor not permitted. †Nivolumab given for a maximum of 2 years. ‡Tumor assessment (RECIST v1.1) at week 10, then every 8 weeks through week 50, then every 12 weeks thereafter. §Discontinuation of one agent did not mandate discontinuation of all agents.

Progression-Free Survival: Final Analysis (PITT Population)



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=276)	116	NR (14.0–NE)
Pbo+Nivo+Ipi (N=274)	133	11.3 (7.7–18.2)

Hazard ratio 0.73 (95% CI 0.57–0.94); p=0.013

Number at Risk

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

PFS per RECIST v1.1 by BIRC.

Data cut-off: Aug 23, 2021

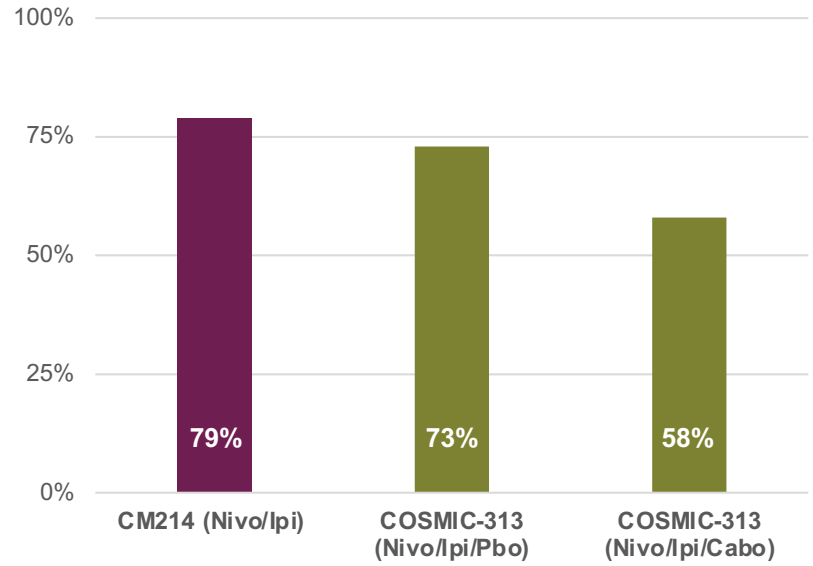
Does toxicity get in the way of treatment?

	Nivo/Ipi (CM214) (N=547)	Cabo/Nivo (9ER) (N=320)	Cabo/Nivo/Ipi (313) (N=428)	Pbo/Nivo/Ipi (313) (N=427)
	Grade 3–4	Grade 3–4	Grade 3–4	Grade 3–4
Treatment-related adverse events				
Any event,* %	47	65	73	41
Alanine aminotransferase increased	5	6	26	6
Aspartate aminotransferase increased	4	4	20	5
Diarrhea	4	7	4	3
Palmar-plantar erythrodysesthesia	<1	8	3	0
Hypothyroidism	<1	<1	<1	0
Hypertension	<1	13	8	2
Fatigue	4	3	2	1
Lipase increased	10	6	9	6
Amylase increased	6	4	5	2
Rash	2	2	2	1
Pruritus	<1	<1	0	<1

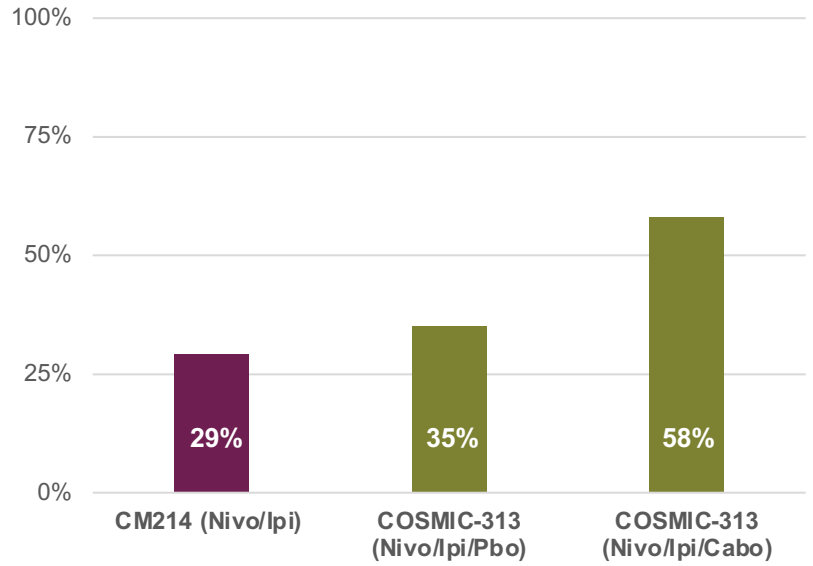
[1]Motzer et al, The Lancet Onc, 2019; [2]Motzer et al, The Lancet Onc, 2022

Does toxicity stand in the way of treatment?

Proportion of patients receiving 4 doses of ipilimumab



Proportion of patients receiving >40 mg of prednisone or equivalent



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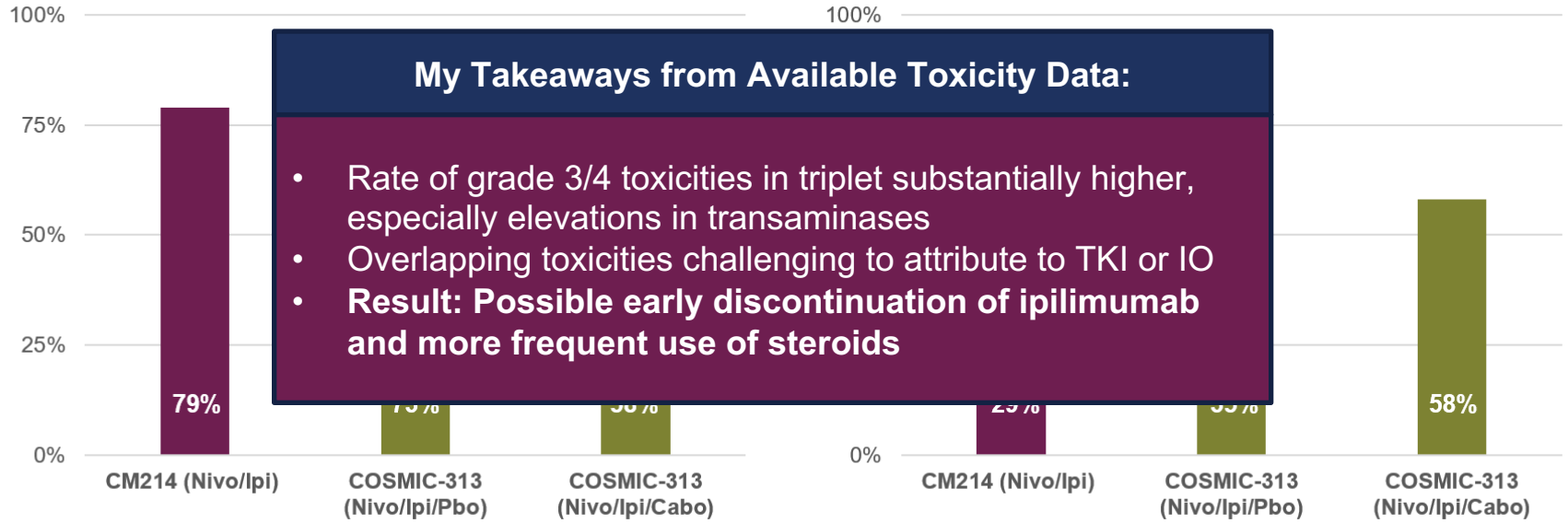


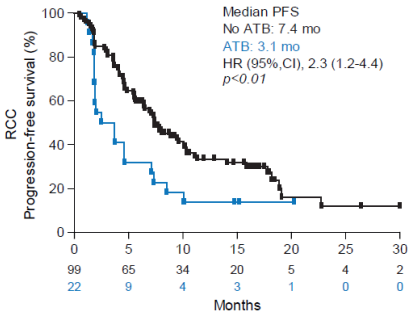
My Takeaways from Available Toxicity Data:

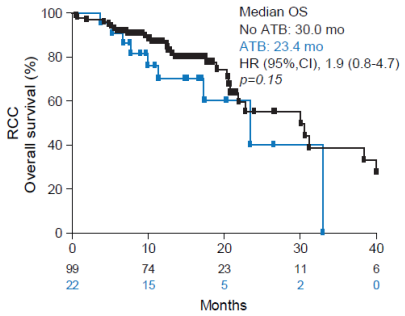
- Rate of grade 3/4 toxicities in triplet substantially higher, especially elevations in transaminases
- Overlapping toxicities challenging to attribute to TKI or IO
- **Result: Possible early discontinuation of ipilimumab and more frequent use of steroids**

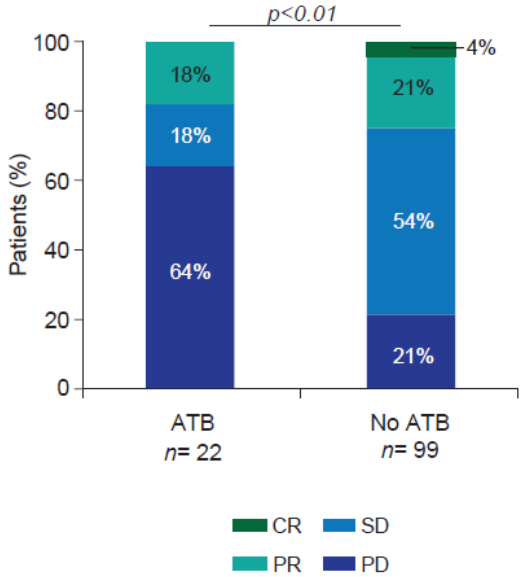
Sumanta K. Pal, MD, FASCO

Microbiome in Renal Cell Carcinoma

Summary:
- 121 pts with kidney cancer
- 239 pts with lung cancer
- Antibiotic use associated with inferior outcome in pts receiving checkpoint inhibitors
- Similar trends in kidney & lung cancer







Treatment-*n* (%)				
	α-PD-(L)1 mAb	106 (88)	14 (88)	92 (88)
	α-PD-(L)1 mAb + α-CTLA-4	10 (8)	1 (6)	9 (8)
	α-PD-(L)1 mAb + Bev	5 (4)	1 (6)	4 (4)

Derosa L *et al* Ann Oncol 2018 (RCC Investigators: DeRosa, Albiges, Escudier)

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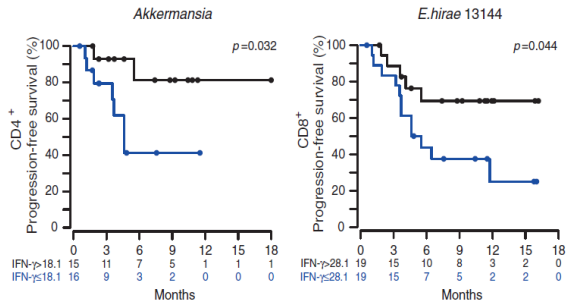
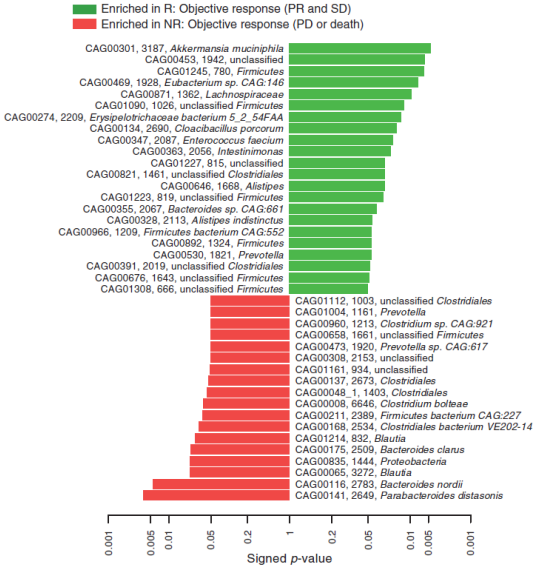
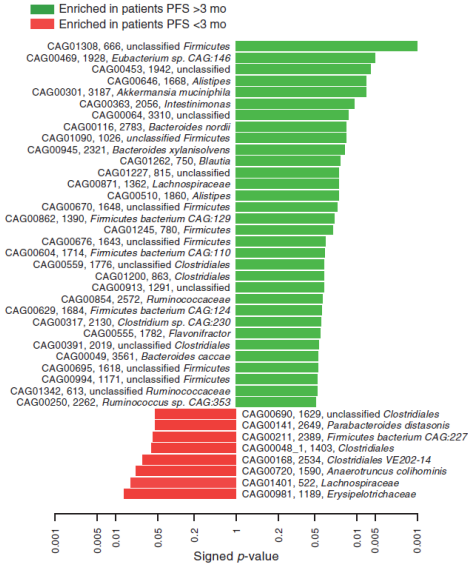
Microbiome in Renal Cell Carcinoma

Summary:

- 60 pts with lung cancer
- 40 pts with kidney cancer
- Baseline and serial stool collections after checkpoint inhibitor initiated
- Specific bacterial species associated with response







Routy B et al Science 2017 (RCC Investigators: DeRosa, Albiges, Escudier)

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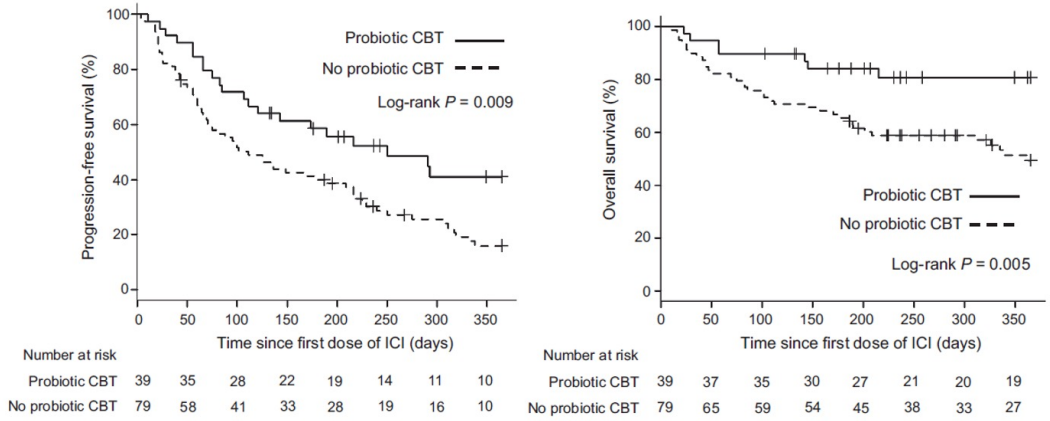
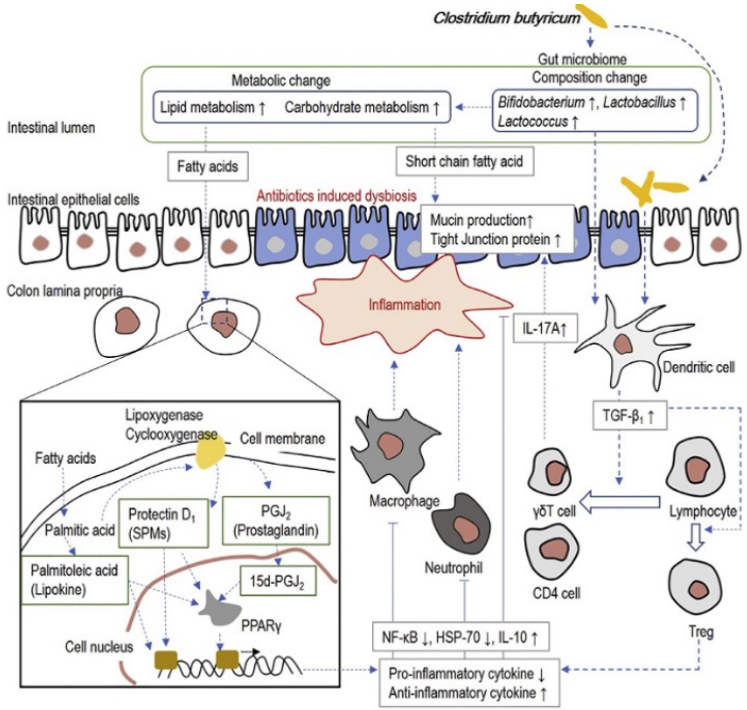
Gut Modulation with CBM-588 in RCC





CBM-588 clinical data and MOA.
CBM-588 may augment the activity of CPIs in NSCLC (*top*), perhaps facilitated by a complex interplay with the immune milieu in the gut (*right*)

Routy et al Science 2018; Tomita et al Cancer Immunol Res 2020; Hagihara et al iScience 2020

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Nivolumab/Ipilimumab + CBM-588: Phase 1B Study

nature medicine

FOCUS | ARTICLES

https://doi.org/10.1038/s41591-022-01694-6

OPEN

Check for updates

Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma: a randomized phase 1 trial

Nazli Dizman[1,2,8], Luis Meza[1,8], Paulo Bergerot[3,8], Marice Alcantara[4], Tanya Dorff[1], Yung Lyou[1], Paul Frankel[5], Yujie Cui[5], Valerie Mira[1], Marian Llamas[1], Joann Hsu[1], Zeynep Zengin[1], Nicholas Salgia[1], Sabrina Salgia[1], Jasnoor Malhotra[1], Neal Chawla[1], Alex Chehrazi-Raffle[1], Ramya Muddasani[1], John Gillece[6], Lauren Reining[6], Jeff Trent[6], Motomichi Takahashi[7], Kentaro Oka[7], Seiya Higashi[7], Marcin Kortylewski[4], Sarah K. Highlander[6] ✉ and Sumanta K. Pal[1] ✉

Dizman, Meza, Bergerot et al Nature Medicine 2022

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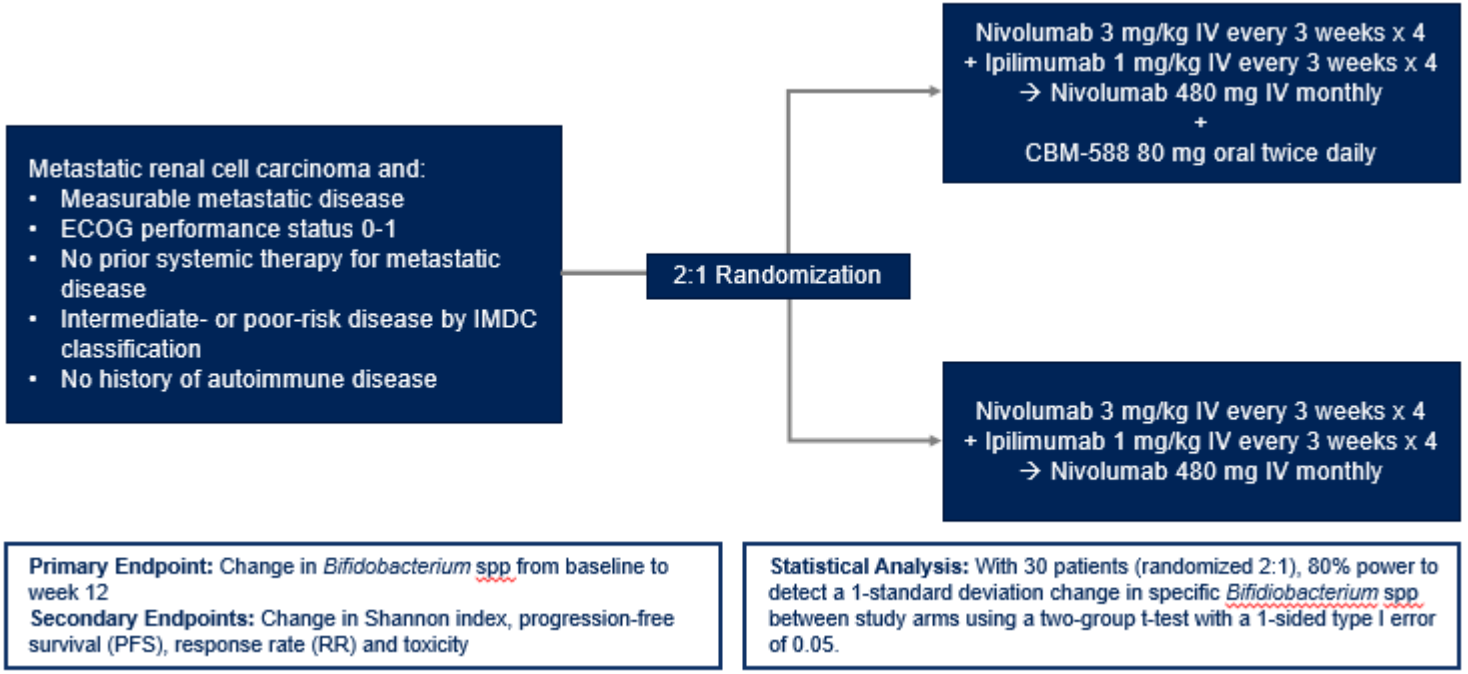
Nivolumab/Ipilimumab + CBM-588: Phase 1B Study



Dizman, Meza, Bergerot et al Nature Medicine 2022

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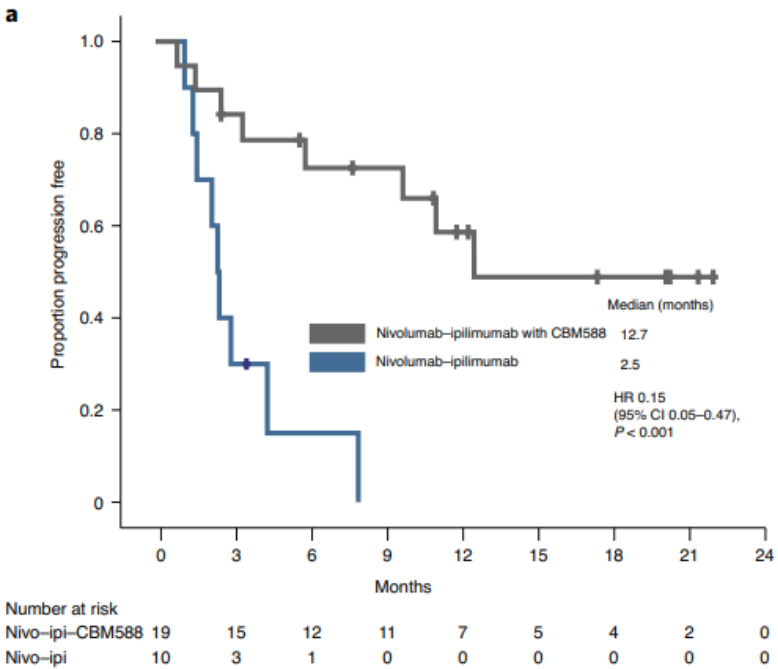
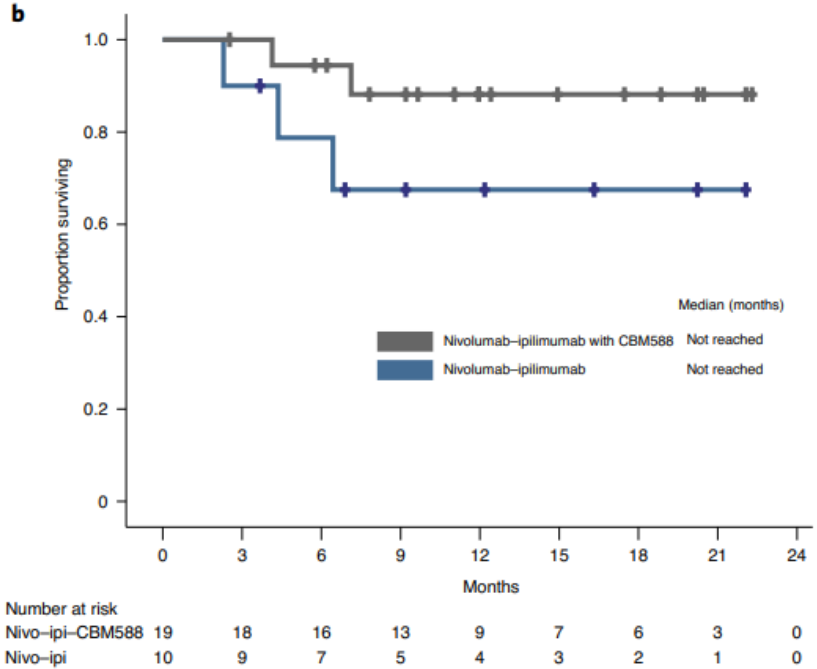
Nivolumab/Ipilimumab + CBM-588: Phase 1B Study





Dizman, Meza, Bergerot et al Nature Medicine 2022

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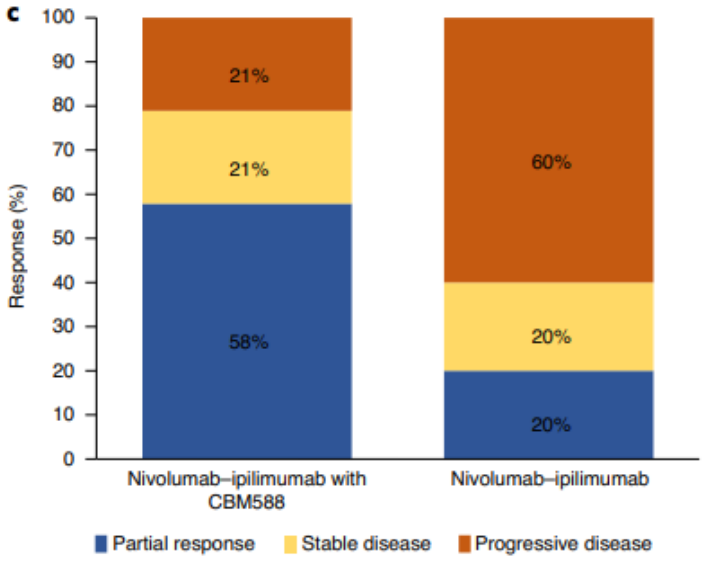
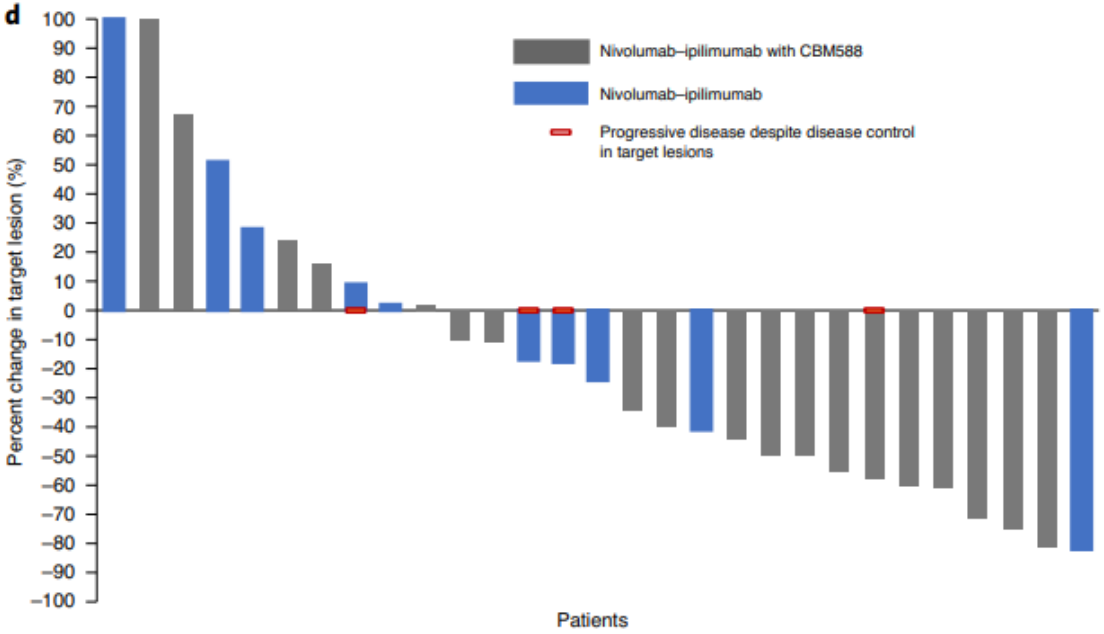
Nivolumab/Ipilimumab + CBM-588: Phase 1B Study





Dizman, Meza, Bergerot et al Nature Medicine 2022

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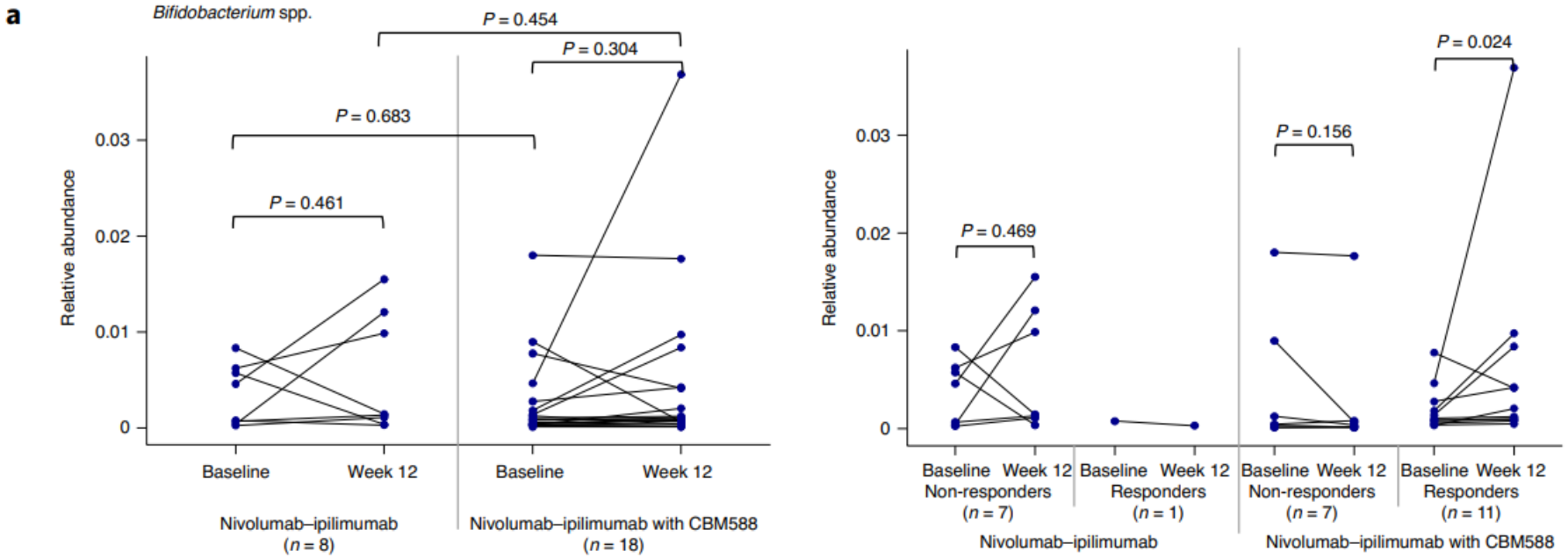
Nivolumab/Ipilimumab + CBM-588: Phase 1B Study



Dizman, Meza, Bergerot et al Nature Medicine 2022

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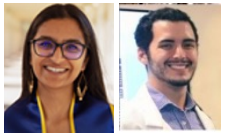
Study Design: IRB 21133 (enrolling now)



Metastatic renal cell carcinoma and:
- Measurable metastatic disease
- ECOG performance status 0-1
- No prior systemic therapy for metastatic disease
- Intermediate- or poor-risk disease by IMDC classification
- No history of autoimmune disease

2:1 Randomization

Cabozantinib 40 mg oral daily +
Nivolumab 480 mg IV monthly
+
CBM-588 80 mg oral twice daily

Cabozantinib 40 mg oral daily +
Nivolumab 480 mg IV monthly

Primary Endpoint: Change in *Bifidobacterium* spp from baseline to week 12
Secondary Endpoints: Change in Shannon index, progression-free survival (PFS), response rate (RR) and toxicity

Statistical Analysis: With 30 patients (randomized 2:1), 80% power to detect a 1-standard deviation change in specific *Bifidiobacterium* spp between study arms using a two-group t-test with a 1-sided type I error of 0.05.

(Published simultaneously in *The Lancet*)

Sunitinib versus cabozantinib, crizotinib or savolitinib in metastatic papillary renal cell carcinoma (pRCC): Results from the randomized phase II SWOG 1500 study

Sumanta K. Pal,[1] Catherine Tangen,[2] Ian Murchie Thompson Jr.,[3] Naomi B. Haas,[4] Daniel J. George,[5] Daniel Yick Chin Heng,[6] Brian M. Shuch,[7] Mark N. Stein,[8] Maria S. Tretiakova,[9] Peter Humphrey,[10] Adebowale Adeniran,[10] Vivek Narayan,[11] Georg A. Bjarnason,[12] Ulka N. Vaishampayan,[13] Ajjai Shivaram Alva,[13] Tian Zhang,[14] Scott Wesley Cole,[15] Melissa Plets,[2] John Wright,[16] Primo N. Lara Jr.[17]

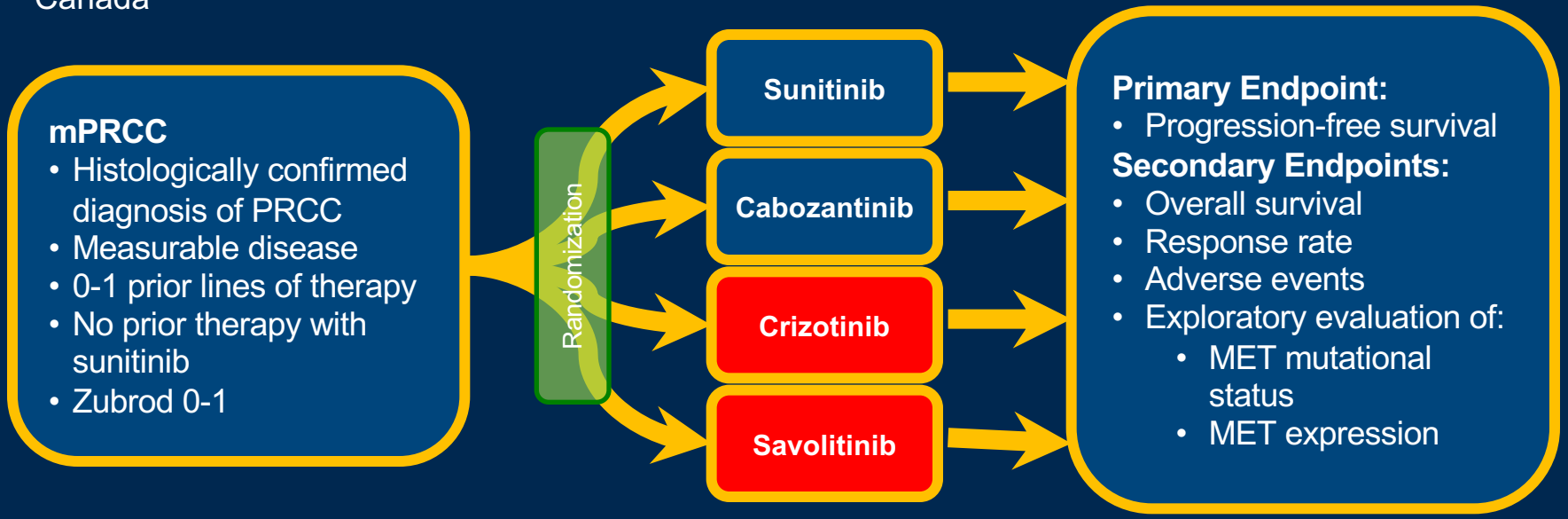
Department of Medical Oncology & Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA;[1] SWOG Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, WA;[2] Christus Santa Rosa Medical Center Hospital, Houson, TX;[3] Abramson Cancer Center, University of Pennsylvania (ECOG-ACRIN), Philadelphia, PA;[4] Duke University Medical Center, Durham, NC;[5] Department of Oncology, Tom Baker Cancer Center, Calgary, AB;[6] Institute of Urologic Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA;[7] Columbia University Medical Center, New York, NY;[8] University of Washington, Seattle, WA;[9] Yale University, New Haven, CT;[10] University of Pennsylvania, Philadelphia, PA;[11] Sunnybrook Odette Cancer Centre (CCTG), Toronto, ON;[12] University of Michigan, Ann Arbor, MI;[13] Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University, Durham, NC;[14] Oklahoma Cancer Specialists and Research Institute (NRG Oncology), Tulsa, OK;[15] National Cancer Institute, Cancer Therapy Evaluation Program, Investigational Drug Branch, Bethesda, MD;[16] UC Davis Comprehensive Cancer Center, Sacramento, CA[17]

PRESENTED AT: Genitourinary Cancers Symposium

#GU21

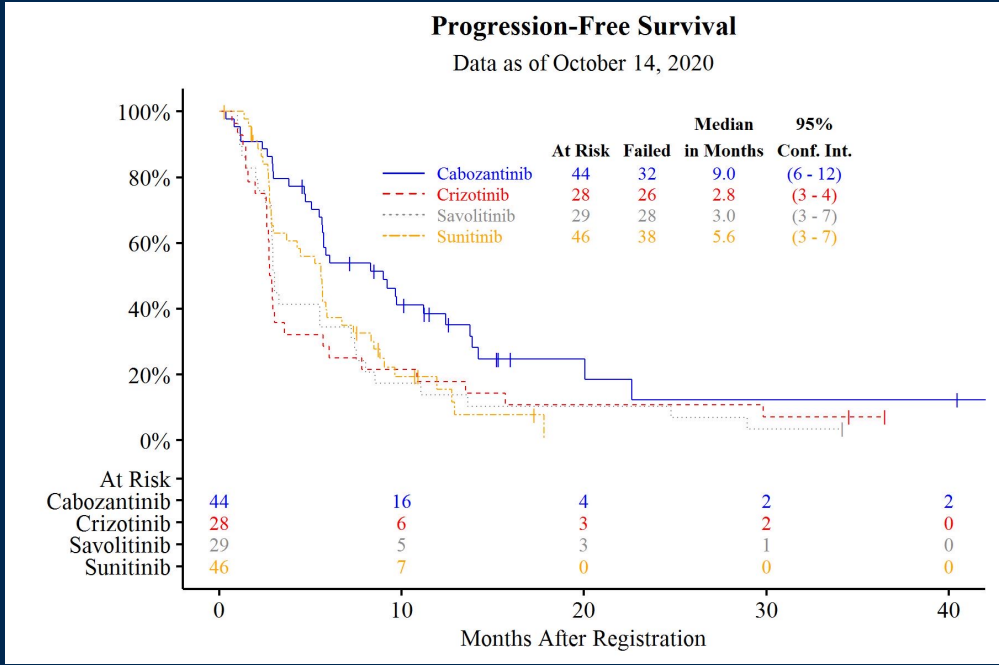
Results: Accrual and Futility Analysis

- From April 2016 to December 2019, 152 patients were enrolled at 65 centers throughout the US and Canada



- Savolitinib and crizotinib arms closed for futility in December of 2018

Results: Progression-Free Survival



- Cabozantinib significantly prolonged PFS relative to sunitinib (HR 0.60 (95%CI 0.37-0.97 [1-sided P-value=0.019])

Concept: Clinical Trial Schema

mPRCC
- Histologically confirmed diagnosis of PRCC
- Measurable disease
- 0-1 prior lines of therapy
- No prior IO or Cabo/Sutent
- Zubrod PS 0-2

Randomize 1:1

- Cabozantinib
- Cabozantinib + Atezolizumab

Primary Endpoint
- Progression-Free Survival

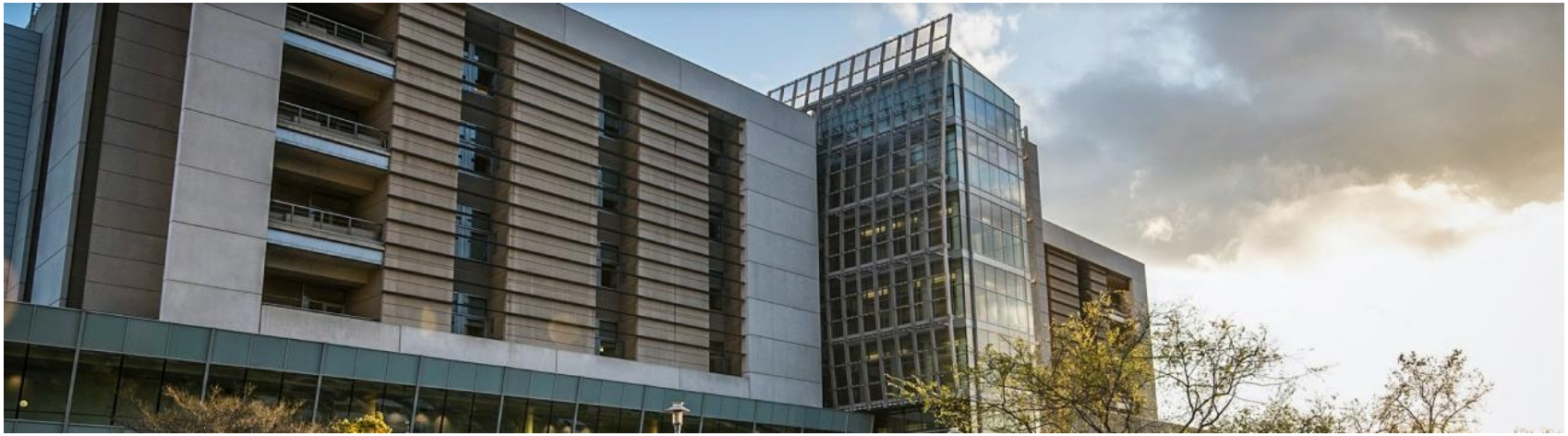
Secondary Endpoints
- Overall Survival
- Objective Response Rate
- Complete Response Rate
- Clinical Outcome by
  - MET mutational/expression status
  - WES (ex. T_{eff}/T_{angio} gene signature)
  - PD-L1/TMB expression

Stratification Factors
- Zubrod Status (0-1 vs 2)
- Histology (Type 1 vs 2 vs NOS)
- Number of Prior Lines of Therapy
- PD-L1 Status (if 3 arm trial)

- PI: Benjamin Maughan, MD
- Co-PI: Sumanta Pal, MD

Thank you for your attention!

Please contact me at spal@coh.org or @montypal.



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