Renal Cell Carcinoma Updates

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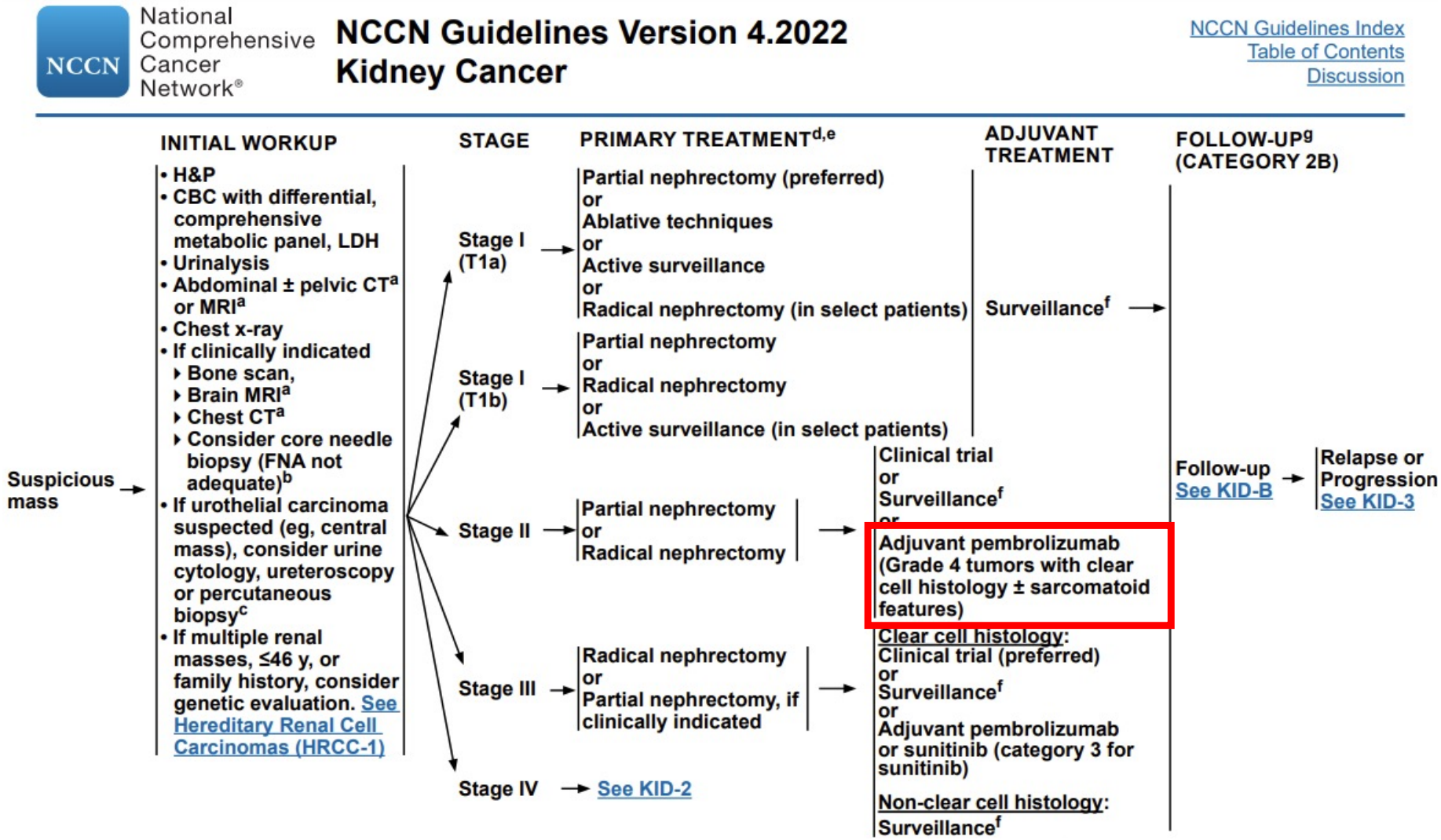
Renal Cell Carcinoma Updates

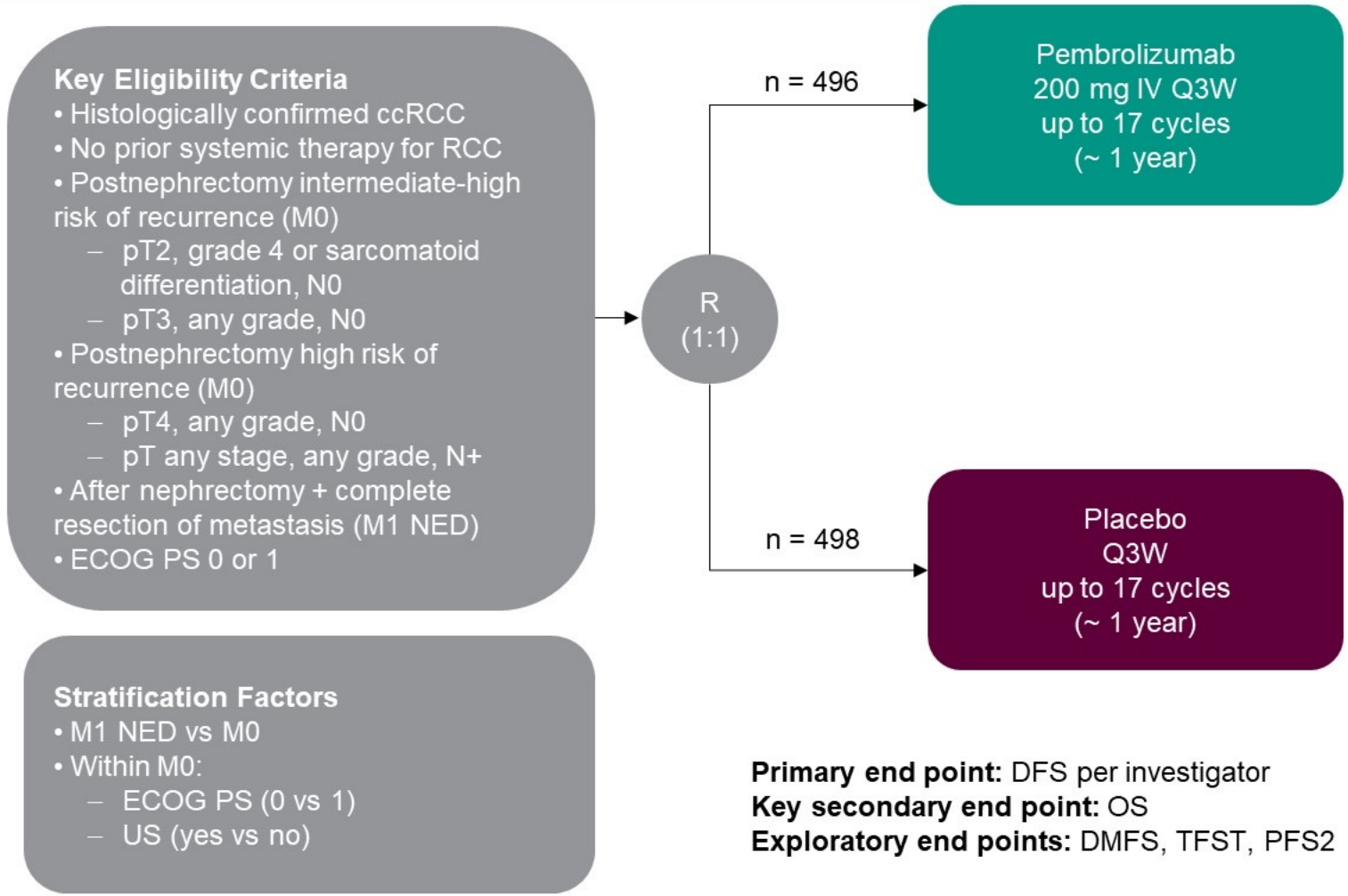
- Adjuvant
- Frontline Options and How to Select
- Refractory Treatment Options
  - Highlight IO refractory subset
- Ongoing Clinical Trials in IO refractory setting
- Clinical Trial Development

Adjuvant Therapy in RCC



Background and Study Design

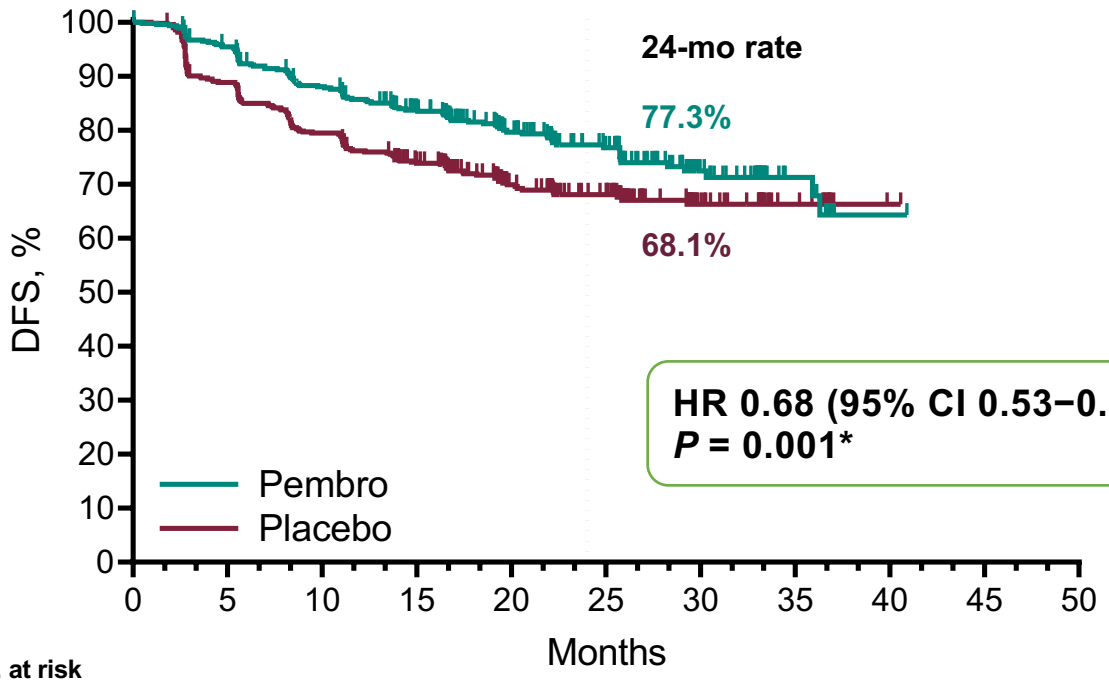
- Results of KEYNOTE-564 showed that adjuvant pembrolizumab improved DFS compared with placebo after a median 30.1 months of follow-up in patients with ccRCC at increased risk for recurrence after nephrectomy[1]
- Post hoc exploratory analyses are presented of
  - Distant metastasis-free survival (DMFS; time to radiographically detectable metastatic disease or any-cause death)
  - Time to first subsequent drug treatment (TFST; time to first subsequent therapy or any-cause death)
  - Time to second progression (PFS2; time from randomization to progression on next-line therapy or any-cause death)
- Median time from randomization to database cutoff was 30.1 months (range, 20.8-47.5 months)



Primary end point: DFS per investigator
Key secondary end point: OS
Exploratory end points: DMFS, TFST, PFS2

Primary Endpoint: DFS, ITT Population

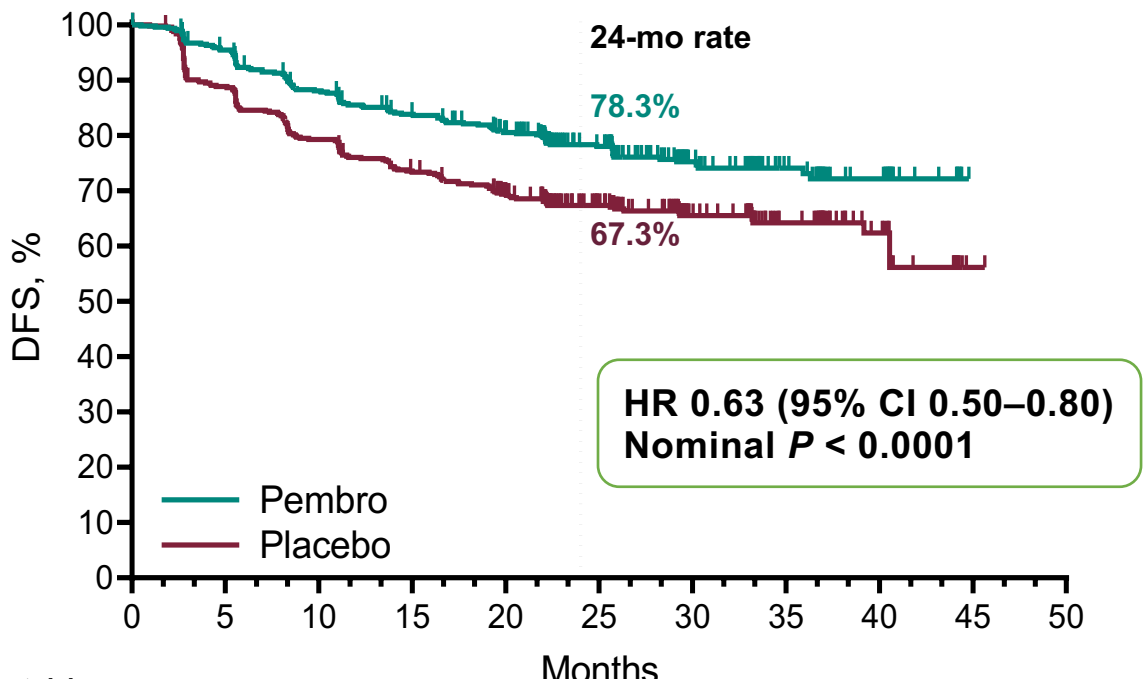
Primary Analysis: 24.1 mo Follow-Up



No. at risk											
Pembro	496	457	414	371	233	151	61	21	1	0	0
Placebo	498	436	389	341	209	145	56	19	1	0	0

	Pts w/ Event	Median, mo (95% CI)
Pembro	109	NR (NR–NR)
Placebo	151	NR (NR–NR)

Updated Analysis: 30.1 mo Follow-Up



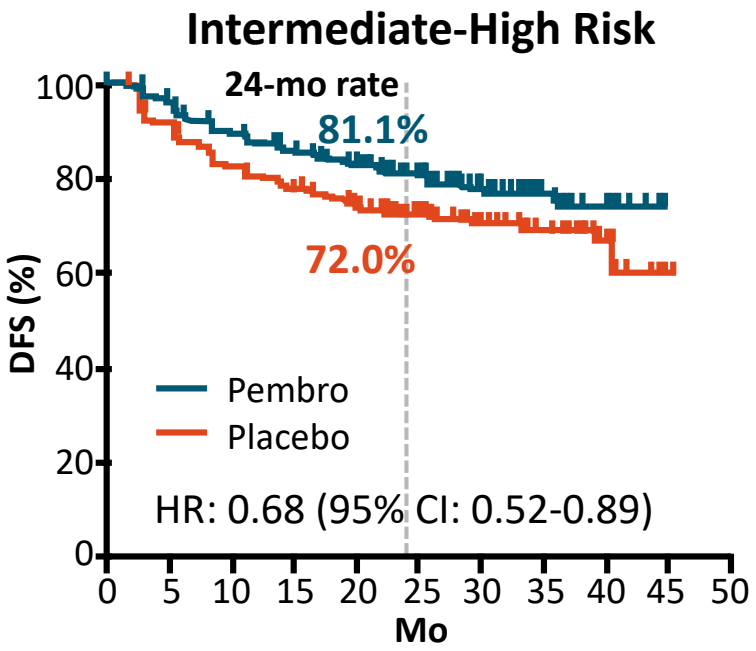
No. at risk											
Pembro	496	458	416	389	361	255	135	77	37	0	0
Placebo	498	437	389	356	325	230	125	74	33	1	0

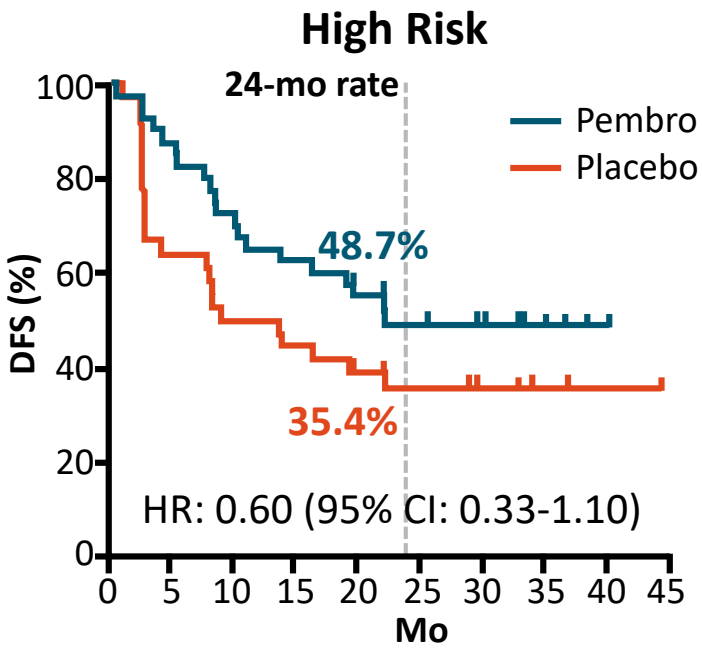
	Pts w/ Event	Median, mo (95% CI)
Pembro	114	NR (NR–NR)
Placebo	169	NR (40.5–NR)

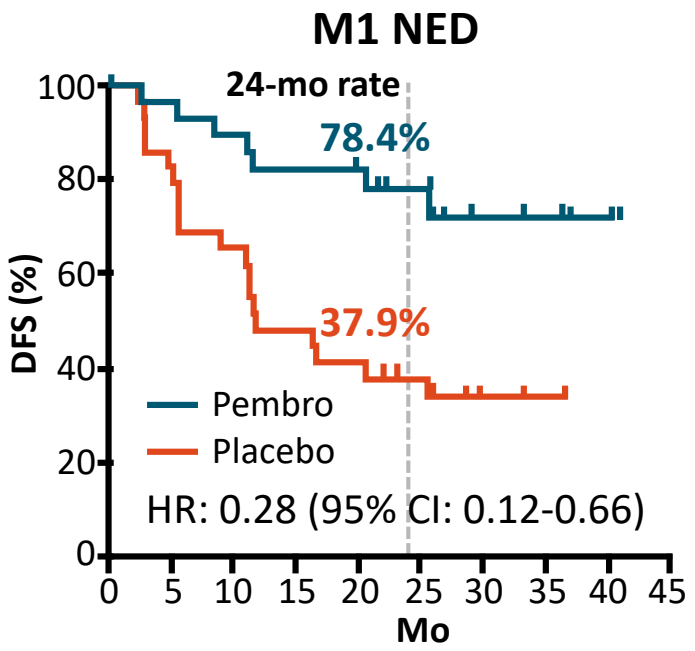
* denotes statistical significance.

ITT population included all randomized participants. DFS, disease-free survival; NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

Keynote-564, 30 month follow-up DFS by recurrence risk







(Choueiri GU ASCO 2022)

Who should get adjuvant therapy?

	Intermediate-High Risk		High Risk		M1 NED
	pT2	pT3	pT4	Any pT	NED after resection of oligometastatic sites ≤1 year from nephrectomy
	Grade 4 or sarcomatoid	Any grade	Any grade	Any grade	
	N0	N0	N0	N+	
	M0	M0	M0	M0	
Risk of recurrence at 5 years	**31%**	**47%**	**54%**	**63%**	**?70%**
Abs. reduction	10%	15%	17%	20%	24%
OS at 5 years	82%	77%	63%	54%	?

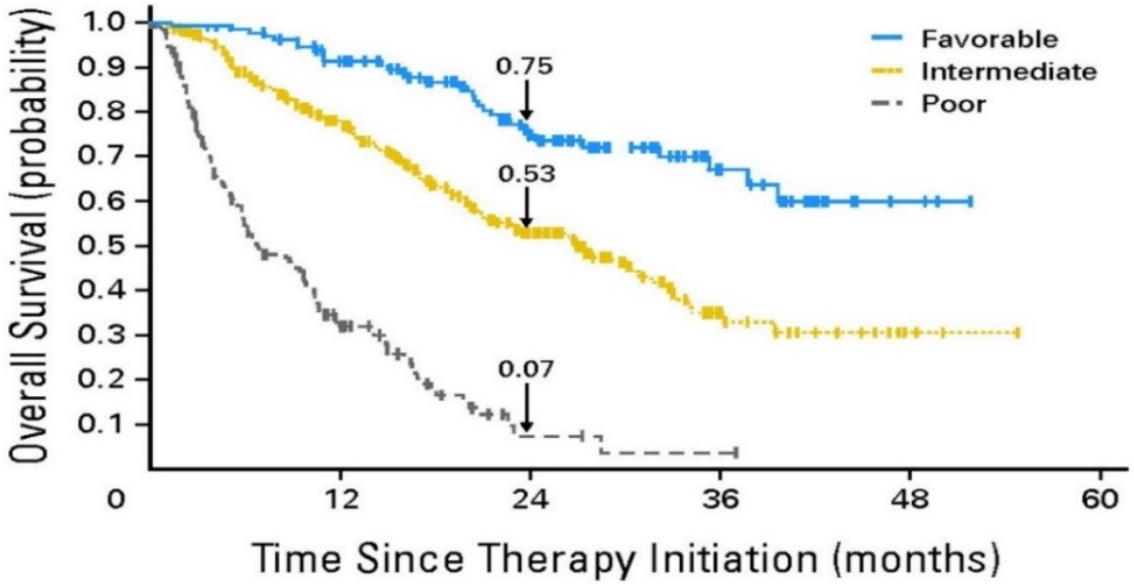
More to come:

Trial	Randomization	Question
PROSPER (ECOG-EA8143)	Neoadj/adj nivolumab vs surgical SoC	Is neoadju**Press release did not meet primary endpoint**ntact kidney tumor safe and does i?
IMMotion010	Adj atezolizumab vs placebo	Is adjuvar**Press release did not meet primary endpoint**han no adjuvant therapy?
KEYNOTE-564	Adj pembrolizumab vs placebo	Is adjuvant PD-1 therapy better than no adjuvant therapy?
Checkmate-914	Adj nivolumab + ipilimumab vs nivolumab alone vs placebo	Is dual PD-1/CTLA-4 inhibition better than mono adjuvant PD-1 therapy**Press release did not meet primary endpoint**
RAMPART	Adj durvalumab + tremelimumab vs durvalumab vs placebo	Is dual PD-L1/CTLA-4 inhibition better than mono adjuvant PD-L1 therapy or no therapy?

(adopted from Naomi Haas)

International Metastatic Database Consortium Risk Stratification

- **Clinical**
  - KPS < 80%
  - Time from diagnosis to treatment < 1 year
- **Laboratory**
  - Hemoglobin < LLN
  - Calcium > ULN
  - Neutrophil count > ULN
  - Platelet count > ULN



No. of events/No. at risk					
Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

- Favorable: 0 risk factors → means slow-growing and/or VEGF-responsive
- Intermediate: 1-2 risk factors → medium growth rate and somewhat VEGF-responsive
- Poor: 3-6 risk factors → fast-growing and VEGF-unresponsive

- Heng DYC, et al. J Clin Oncol. 2009;27:5794-5799.

Frontline Treatment Options Plentiful in RCC

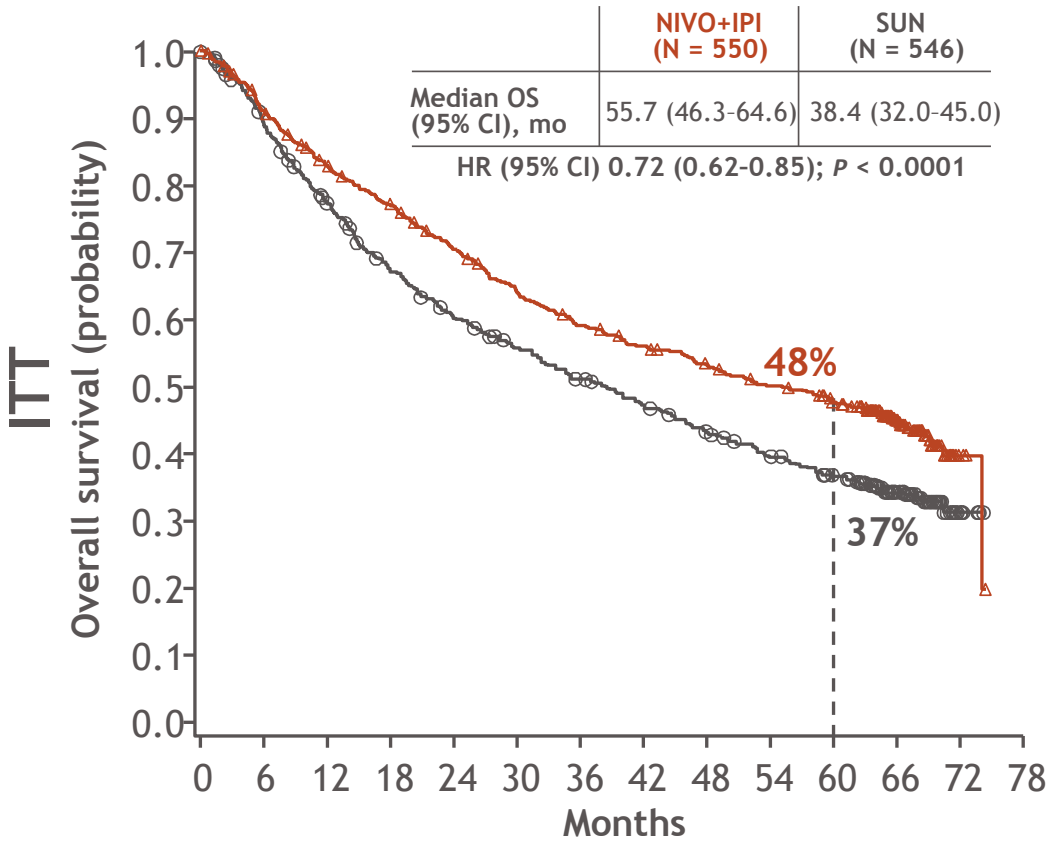
PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances**
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1)	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Ipilimumab + nivolumab[b] • Pazopanib • Sunitinib	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d] (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Ipilimumab + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B) • High-dose IL-2[d] (category 3) • Temsirolimus[e] (category 3)

(NCCN, 2022)

Checkmate 214 ITT: 5-year Update

Overall survival



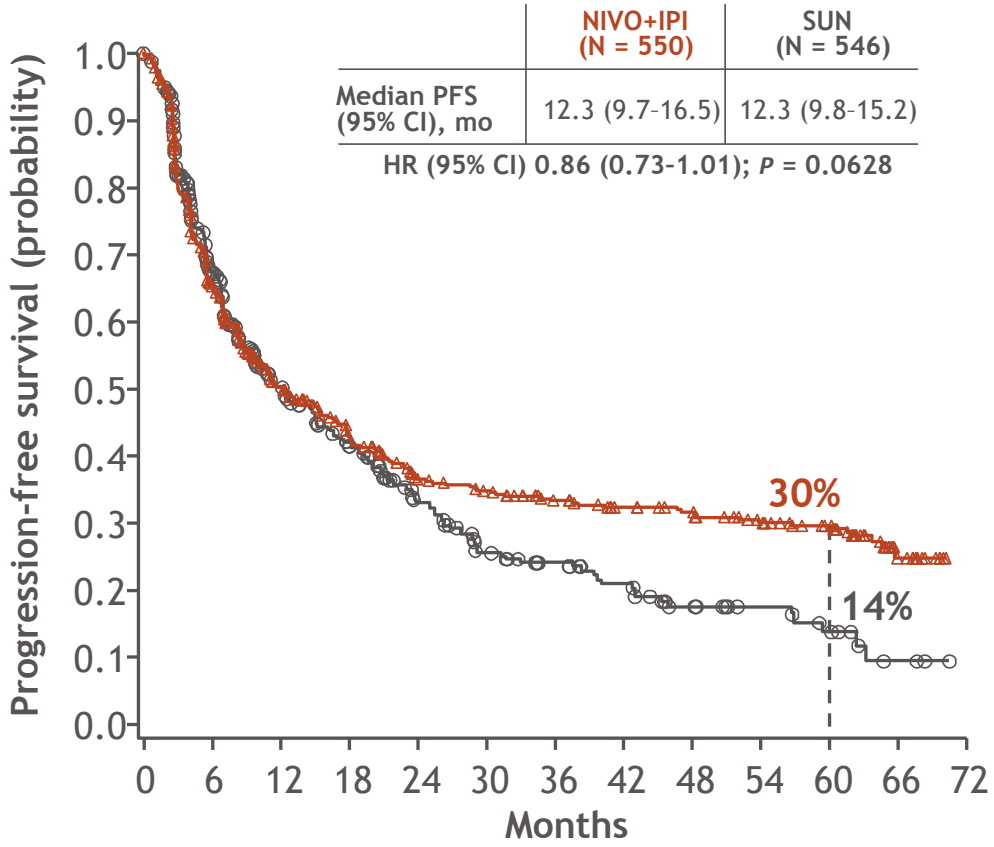
	NIVO+IPI (N = 550)	SUN (N = 546)
Median OS (95% CI), mo	55.7 (46.3-64.6)	38.4 (32.0-45.0)

HR (95% CI) 0.72 (0.62-0.85); *P* < 0.0001

No. at risk

NIVO+IPI	550	493	444	411	372	337	309	291	274	256	236	138	5	0
SUN	546	472	405	347	310	281	257	234	213	192	171	108	6	0

Progression-free survival



	NIVO+IPI (N = 550)	SUN (N = 546)
Median PFS (95% CI), mo	12.3 (9.7-16.5)	12.3 (9.8-15.2)

HR (95% CI) 0.86 (0.73-1.01); *P* = 0.0628

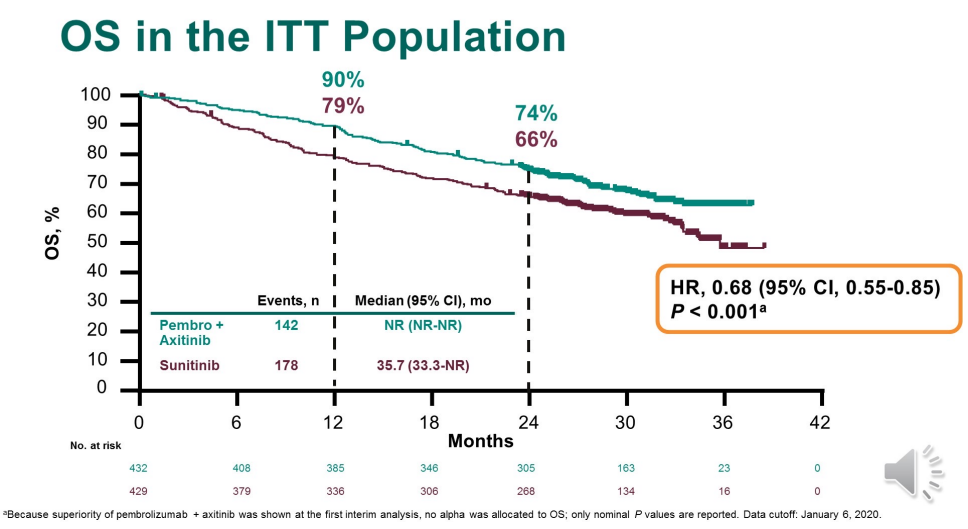
No. at risk

NIVO+IPI	550	315	217	171	132	121	103	92	86	75	62	14	0	
SUN	546	285	178	130	87	59	42	33	21	15	10	3	0	

Motzer RJ et al. ESMO 2021. Abstract 661P.

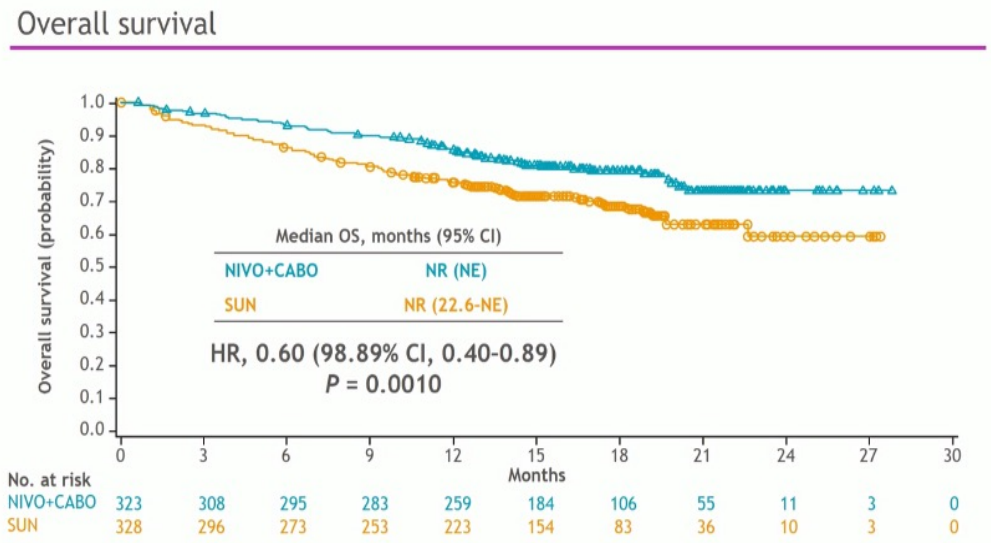
TKI+IO Overall Survival

Keynote 426: Pembro+Axitinib

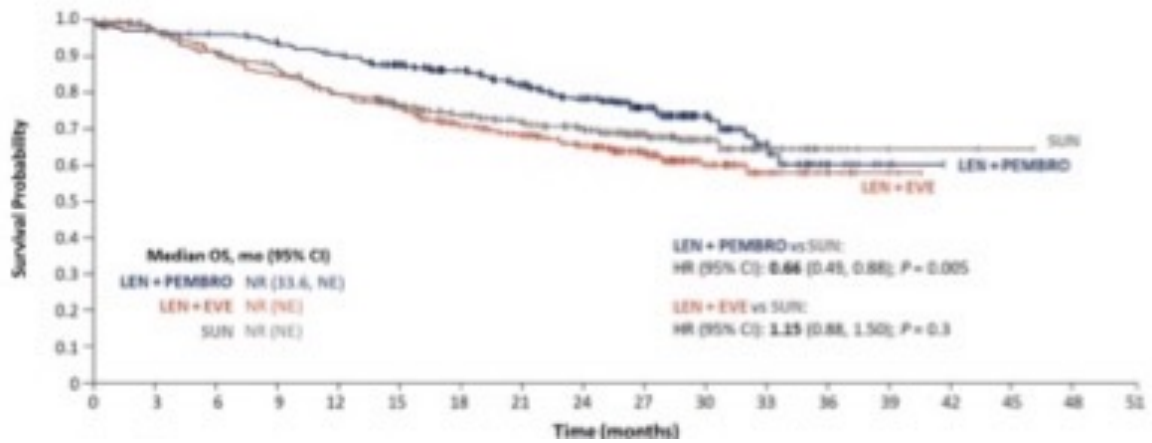


aBecause superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 6, 2020.

Checkmate 9ER: Nivo+Cabozantinib



CLEAR: Pembro+ Lenvatinib



Frontline Treatment Data in RCC

	CheckMate 214[1] Ipi/Nivo vs Sun (n = 550 vs n = 546)	KEYNOTE-426[2] Axi/Pembro vs Sun (n = 432 vs n = 429)	CheckMate 9ER[3] Cabo/Nivo vs Sun (n = 323 vs n = 328)	CLEAR[4] Len/Pembro vs Sun (n = 355 vs n = 357)
mOS, mo HR (CI)	55.7 vs 38.4 **0.72** (0.62-0.85)	45.7 vs 40.1 **0.73** (0.60-0.88)	37.7 vs 34.3 **0.70** (0.55-0.90)	NR vs NR **0.72** (0.55-0.93)
Landmark OS 12 mo Landmark OS 24 mo	**83%** vs 78% **71%** vs 61%	**90%** vs 79% **74%** vs 66%	**86%** vs 76% (est.) **70.3%** vs 60.3%	**90%** vs 79% (est.) **79%** vs 70%
mPFS, mo HR (CI)	**12.2** vs 12.3 0.86 (0.73-1.01)	**15.7** vs 11.1 0.68 (0.58-0.80)	**16.6** vs 8.3 0.56 (0.46-0.68)	**23.9** vs 9.2 0.39 (0.32-0.49)
ORR, %	**39** vs 32	**60** vs 40	**56** vs 28	**71** vs 36
CR, %	**12** vs 3	**10** vs 4	**12** vs 5	**16** vs 4
Median f/u, mo	**67.7**	**42.8**	**32.9**	**33.7**
Primary PD, %	**18**	**11**	**6**	**5**
Prognostic risk, % ▪ Favorable ▪ Intermediate ▪ Poor	 23 61 17	 32 55 13	 23 58 19	 31 59 9
Prior nephrectomy, %	82	83	69	74
Subsequent systemic tx for Sun arm, %	Overall (68) IO (42)	Overall (69) IO (48)	Overall (40) IO (29)	Overall (71) IO (53)
Tx discontinuation due to AEs, %	23 vs 13	20 vs 18	27 vs 10	18.5 (len) / 25 (pembro) / 9.7 (len + pembro) vs 10

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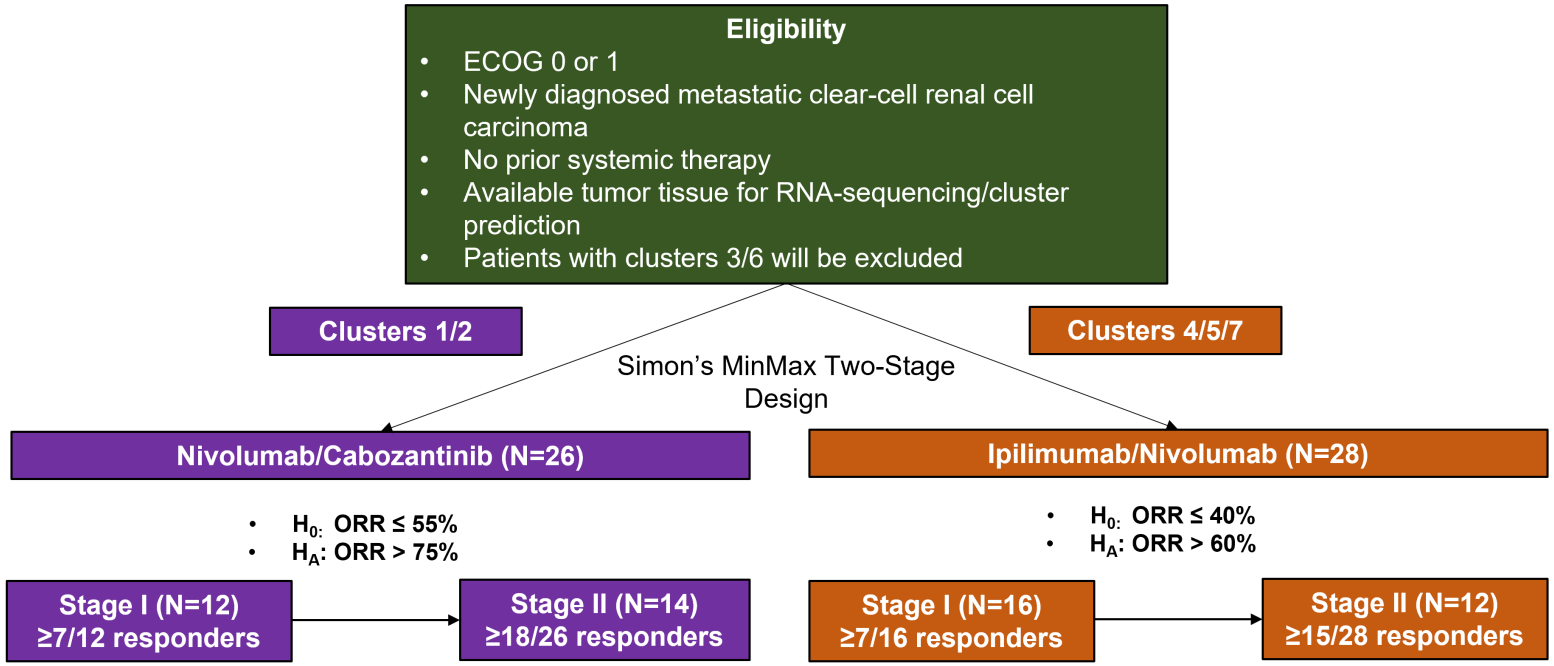
Future Frontline Advances?

- Will a triplet therapy have improved clinical benefit and will it be safe?
- Are other mechanisms of action important in the frontline? Metabolic inhibitors, LAG3, TIGIT?
- Can we select patients based on gene expression data for frontline therapy

Phase II, open-label, parallel single-arm study using tumor RNAseq cluster to assign protocol treatment

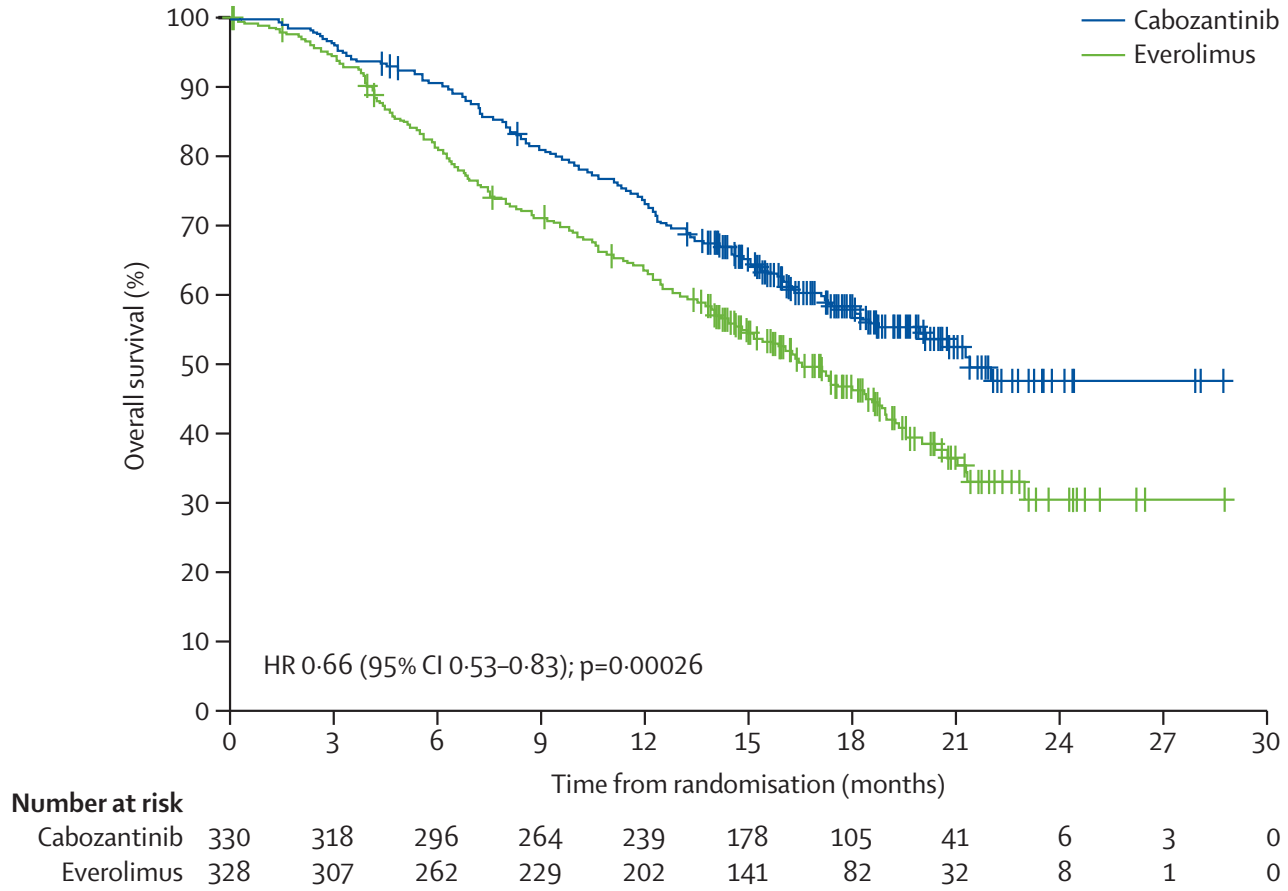


Treatment for Refractory Clear Cell Histology

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Cabozantinib (category 1) • Lenvatinib + everolimus (category 1) • Nivolumab[b] (category 1)	• Axitinib (category 1) • Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Tivozanib[g] • Axitinib + avelumab[b] (category 3)	• Everolimus • Bevacizumab[f] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Sorafenib (category 3) • Temsirolimus[e] (category 2B)

(NCCN, 2022)

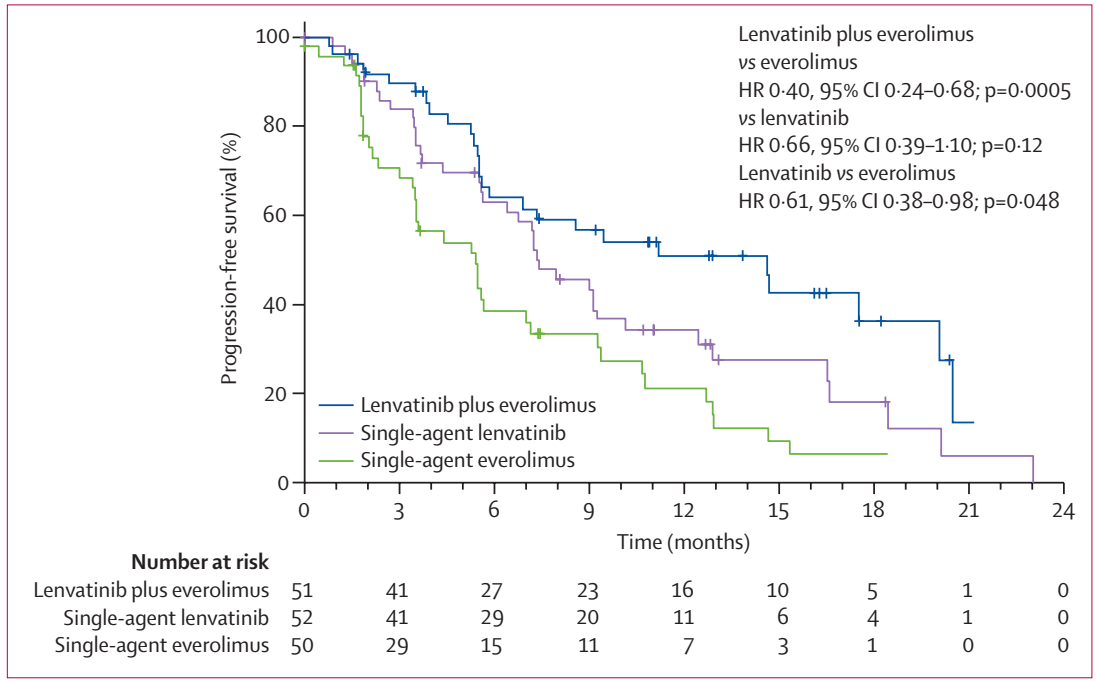
Ph 3 METEOR Trial: Cabozantinib vs Everolimus after prior VEGF TKI

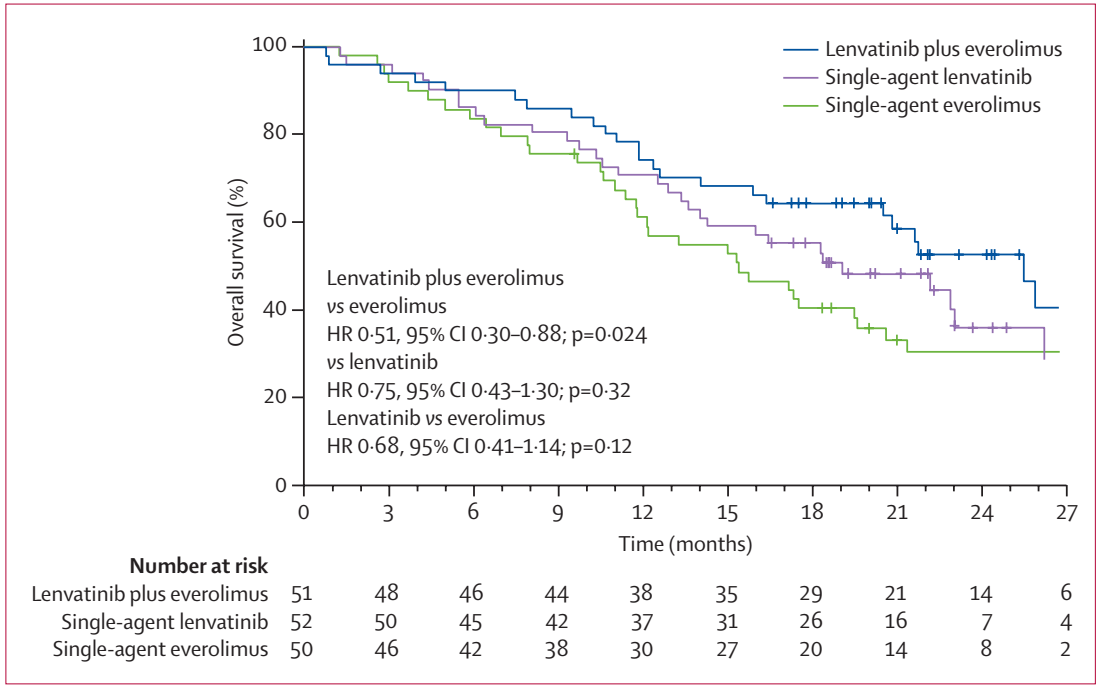


- 5% of patients had prior IO
- ORR with cabozantinib: 17% vs 3% with everolimus alone

(Choueiri et al., 2016)

Randomized Ph 2: Lenvatinib, Everolimus or Combination after prior VEGF TKI

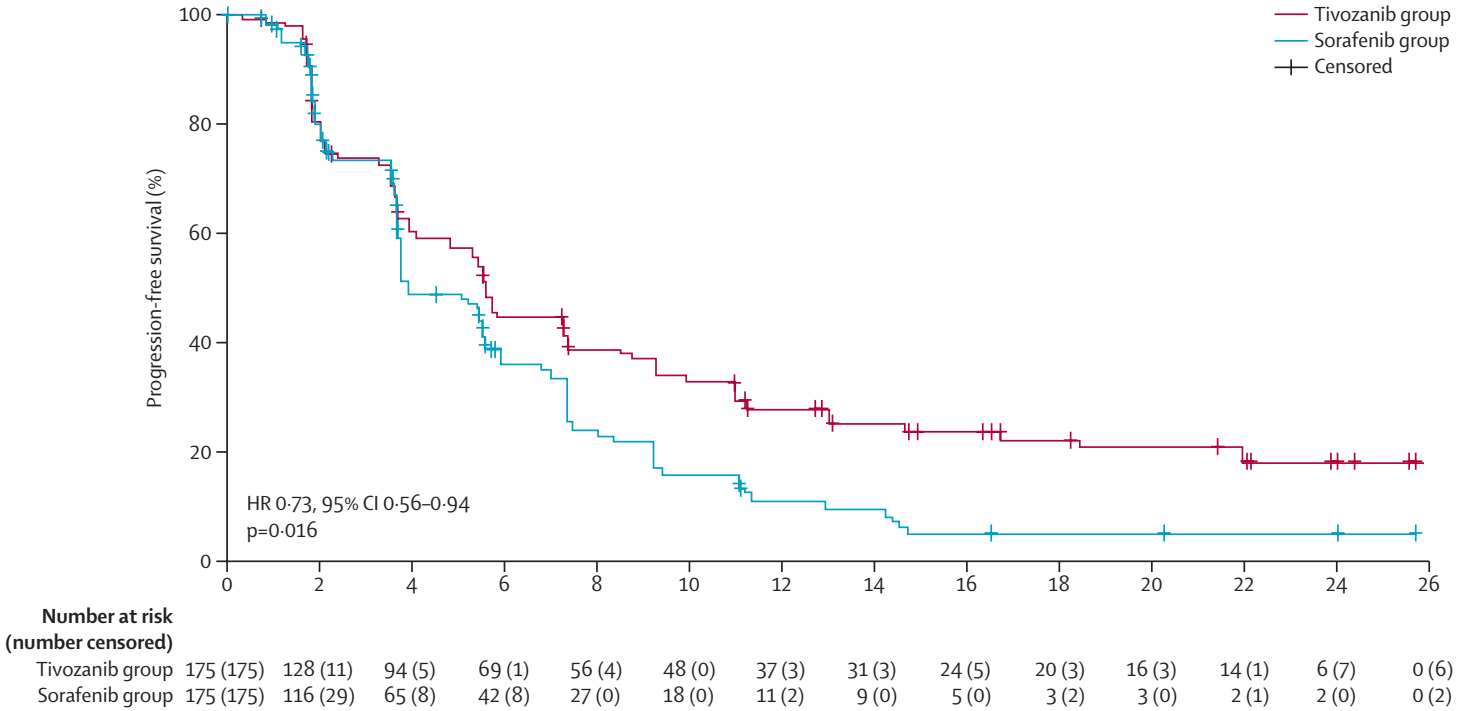




- 3% with prior ICI treatment
- ORR with lenvatinib + everolimus: 43% vs 6% with everolimus alone

(Motzer et al., 2015)

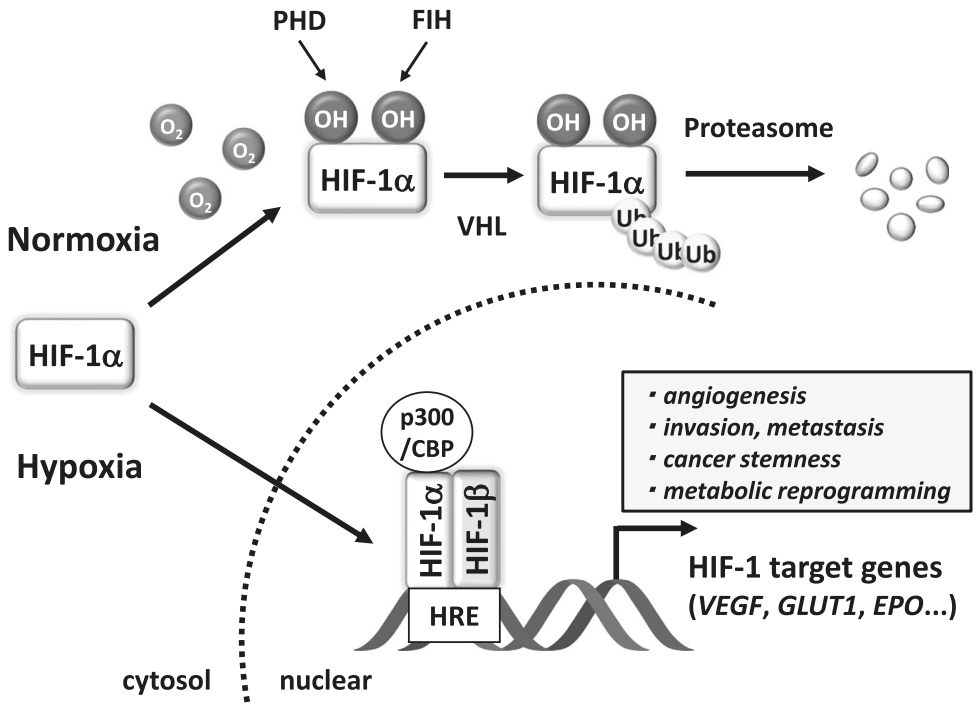
Randomized Ph 3: Tivozanib vs sorafenib in refractory RCC



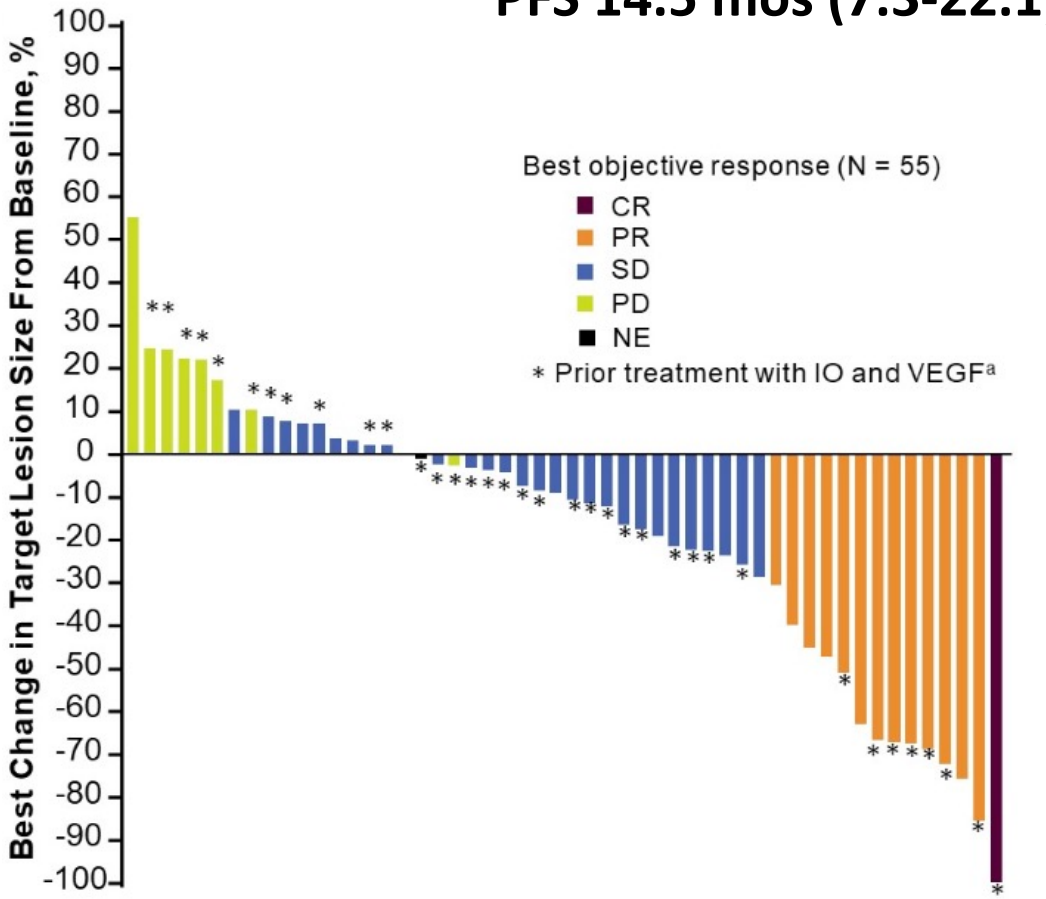
- 26% Prior ICI and TKI
- ORR: 18% with tivozanib vs 8% with sorafenib
- Average 60% patients with 2 prior therapies, 40% treated with 3 prior therapies

(Rini et al., 2020)

Ongoing Trials: Targeting HIF in RCC



PFS 14.5 mos (7.3-22.1)

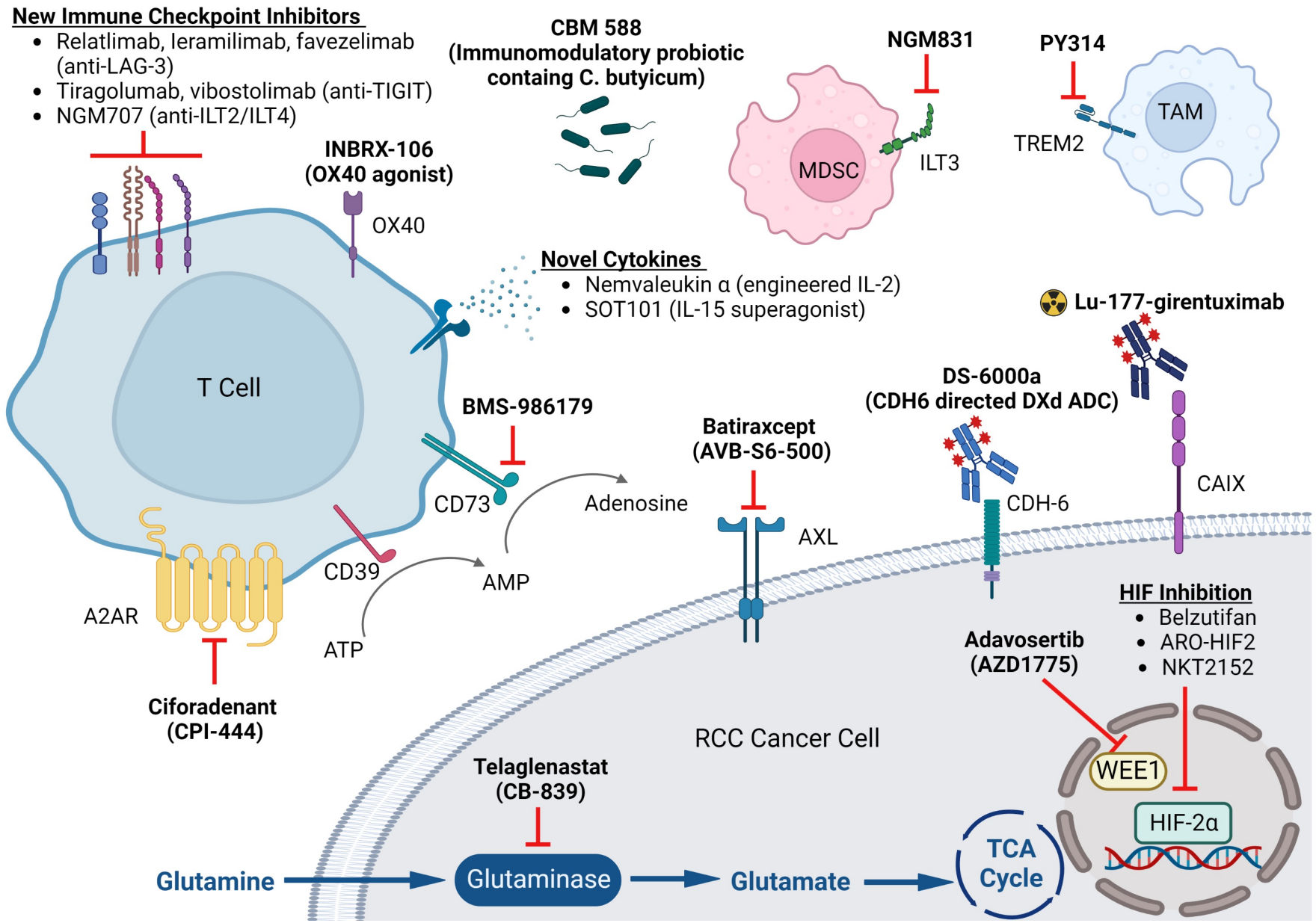


(Ikeda and Kakeya et al., 2021; Jonasch ASCO 2022)

Ongoing Clinical Trials in the Refractory IO setting

Title	Inclusion	Treatment Arms
MK-6482-005: Phase III Trial of Belzutifan vs Everolimus in Advanced RCC After PD-1/PD-L1 and TKI Therapy (n = 736)[1]	▪ Clear-cell RCC ▪ Prior therapy with PD-1/PD-L1 inhibitor and VEGF TKI, as monotherapy or in combination ▪ ≤3 prior therapies	Belzutifan vs Everolimus
CONTACT-03: Phase III Trial of Atezo + Cabo vs Cabo in Advanced RCC After PD-1/PD-L1 Therapy (n = 500)[2]	▪ Clear-cell RCC or non–clear-cell RCC (papillary or unclassified) ▪ Prior first- or second-line therapy with PD-1/PD-L1 inhibitor as immediate preceding therapy ▪ No more than 1 previous PD-1/PD-L1 inhibitor	Atezolizumab + cabozantinib vs Cabozantinib
TiNivo-2: Phase III Trial of Tivozanib + Nivolumab vs Tivozanib in Advanced RCC After IO Therapy (n = 326)[3]	▪ Clear-cell RCC ▪ PD during or following ≥6 wk of treatment with an IO therapy ▪ ≤2 previous lines of therapy	Nivolumab + tivozanib vs Tivozanib

Novel Targets and Drug Development in RCC



(Chen, Rini, and Beckermann, unpublished, figure made with BioRender)