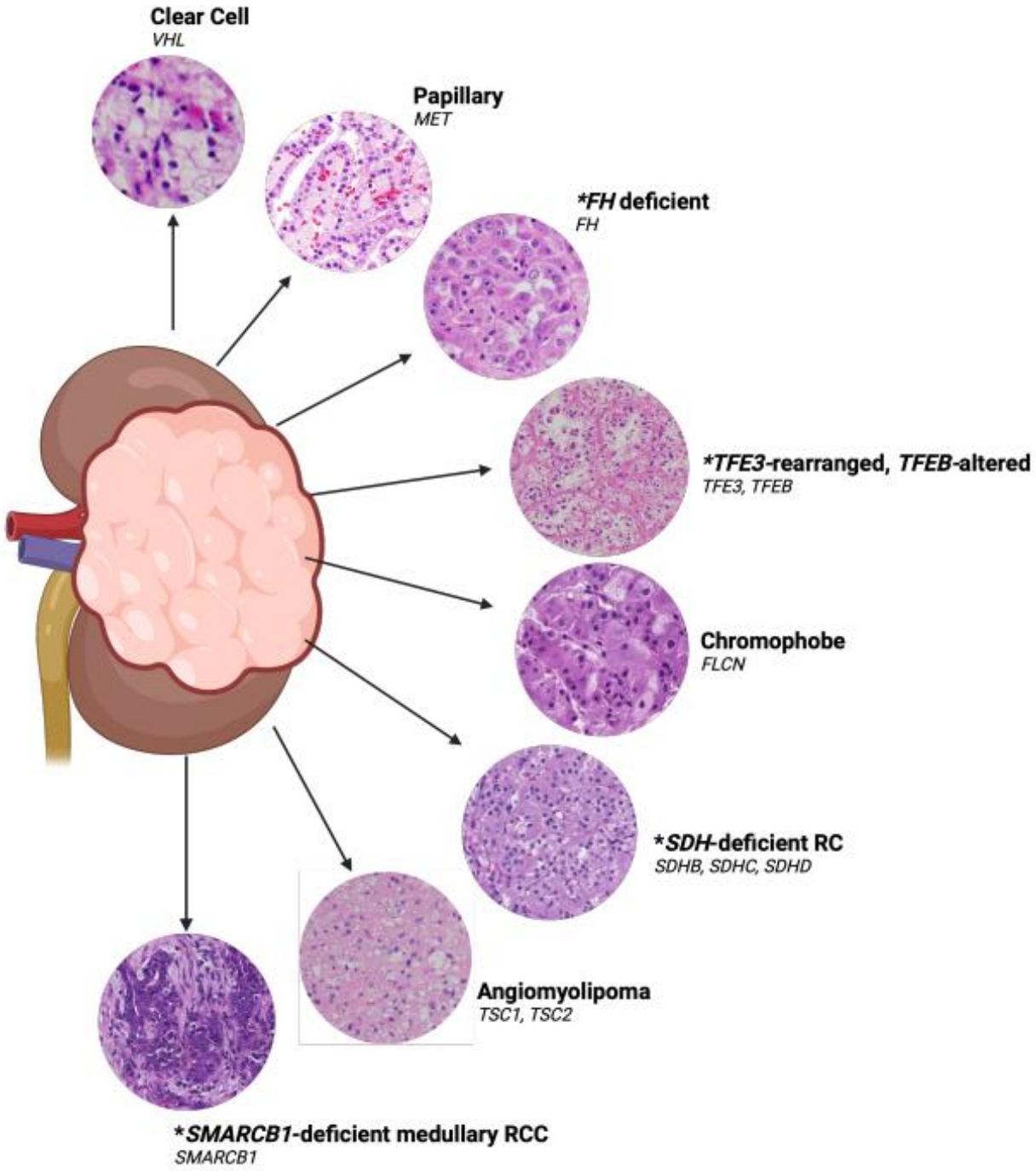
Kidney Cancer: Targeted and Immunotherapy Approaches

14th Annual Winter Cancer Symposium

Catherine Fahey

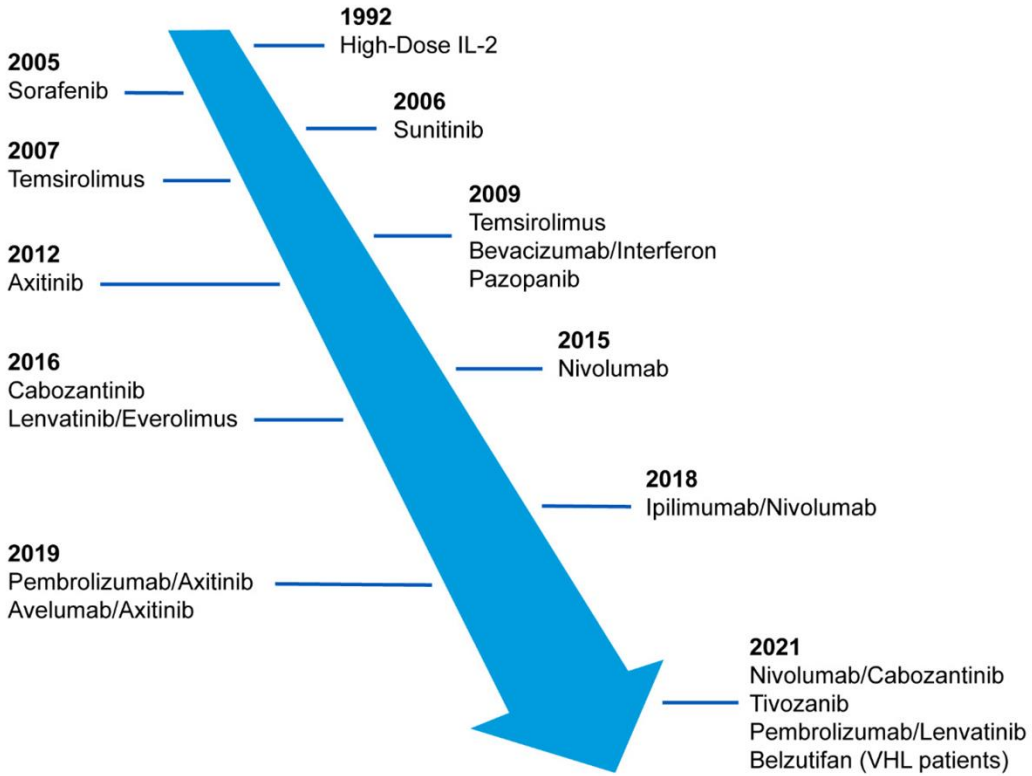
03/01/2025



Kidney cancer consists of multiple histologic subtypes

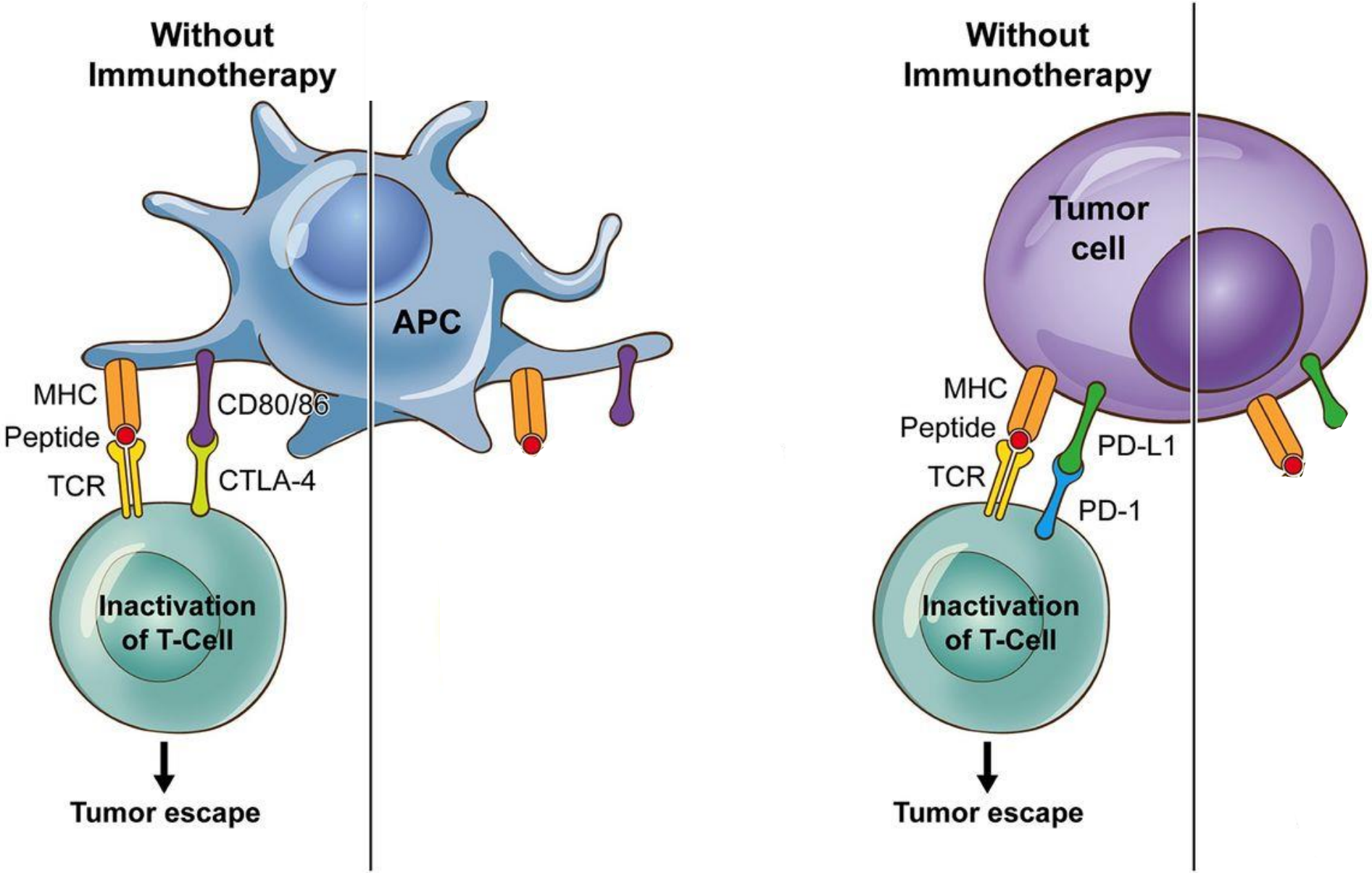
- Clear cell renal cell carcinoma is the most common type of kidney cancer and the most well studied
- FH deficient, TFE-rearranged SDH-deficient and SMARCB1 deficient are molecularly defined

ICI and targeted therapies have revolutionized the treatment of ccRCC

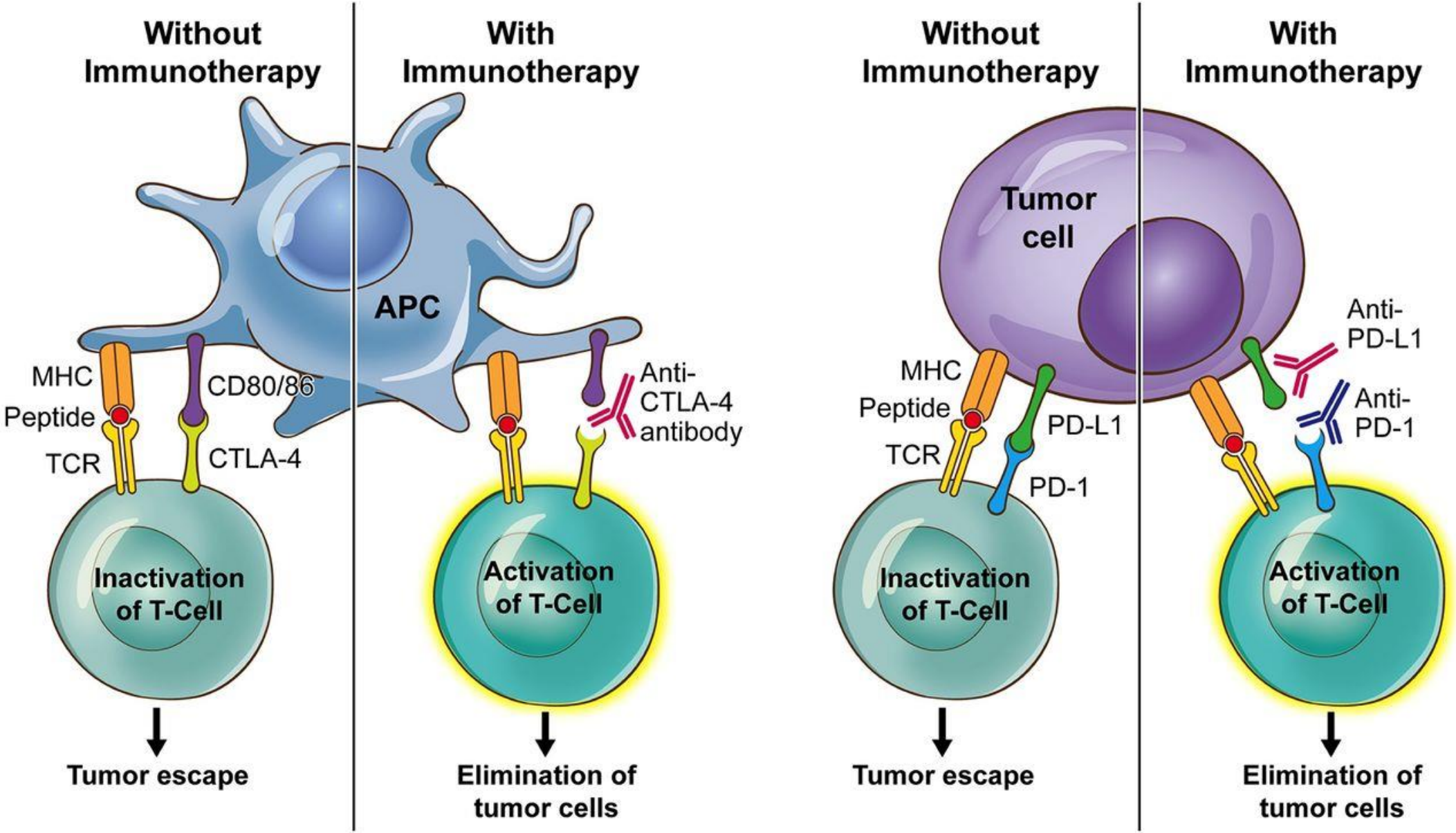


Date	Drug name	Indication	Treatment line
Mar 2011	Ipilimumab	Melanoma	Refractory
Sep 2014	Pembrolizumab	Melanoma	2nd line
Dec 2014	Nivolumab	Melanoma	Refractory
Mar 2015	Nivolumab	SqCC NSCLC	2nd line
Oct 2015	Nivolumab + ipilimumab	BRAF V600 wild-type melanoma	1st line
Oct 2015	Pembrolizumab	NSCLC	2nd line
Oct 2015	Nivolumab	Non-SqCC NSCLC	2nd line
Nov 2015	Nivolumab	RCC	2nd line
Apr 2018	Nivolumab + ipilimumab	Intermediate-/poor-risk RCC	1st line
Apr 2019	Pembrolizumab + axitinib	RCC	1st line
May 2019	Avelumab + axitinib	RCC	1st line
Jan 2021	Nivolumab + cabozantinib	RCC	1st line
Aug 2021	Pembrolizumab + lenvatinib	RCC	1st line

Kase et al. Cancers, 2023. PMID: 36765622
Lee, Kim and Ha. Immune Netw. 2022. PMID 35291660

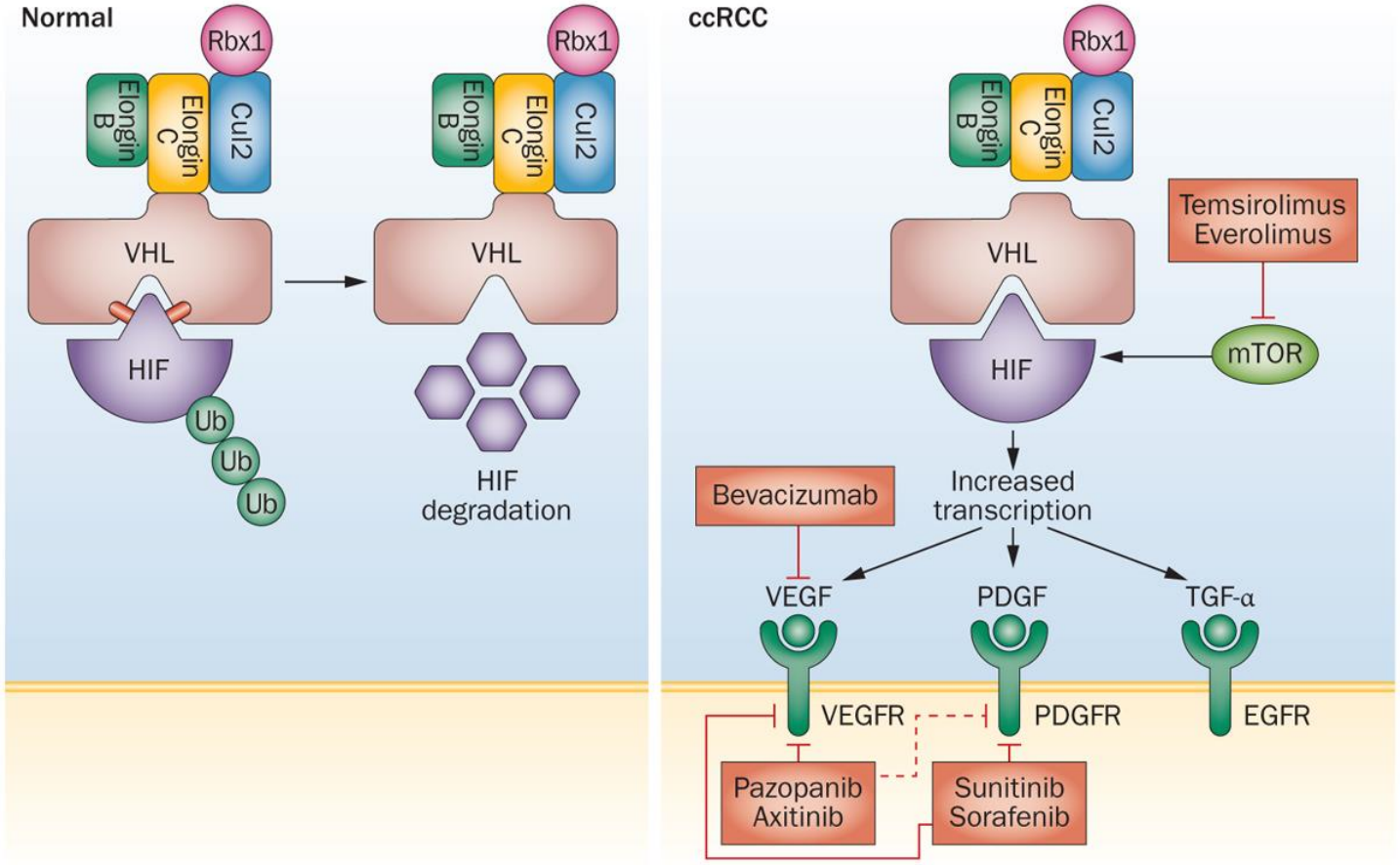


Lewis et al. Br J Anaesth. 2020. PMID: 32007241



Lewis et al. Br J Anaesth. 2020. PMID: 32007241

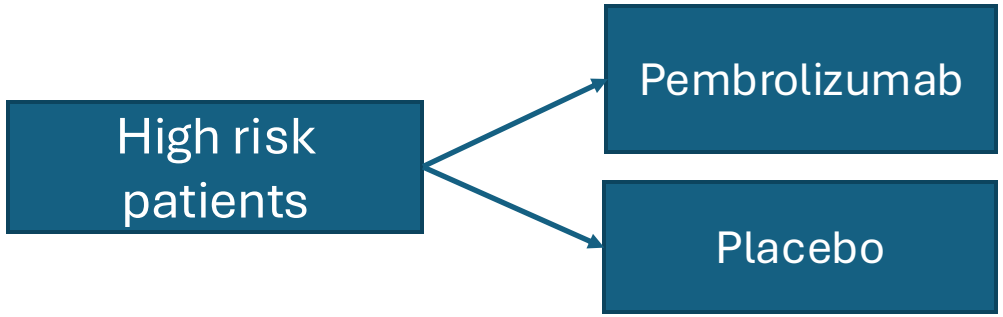
Targeted therapies affect pathways necessary for ccRCC development



Linehan et al, Nat Rev Clin Oncol. PMID: 24129349

What is the role of immunotherapy and targeted therapy in high risk ccRCC after nephrectomy?

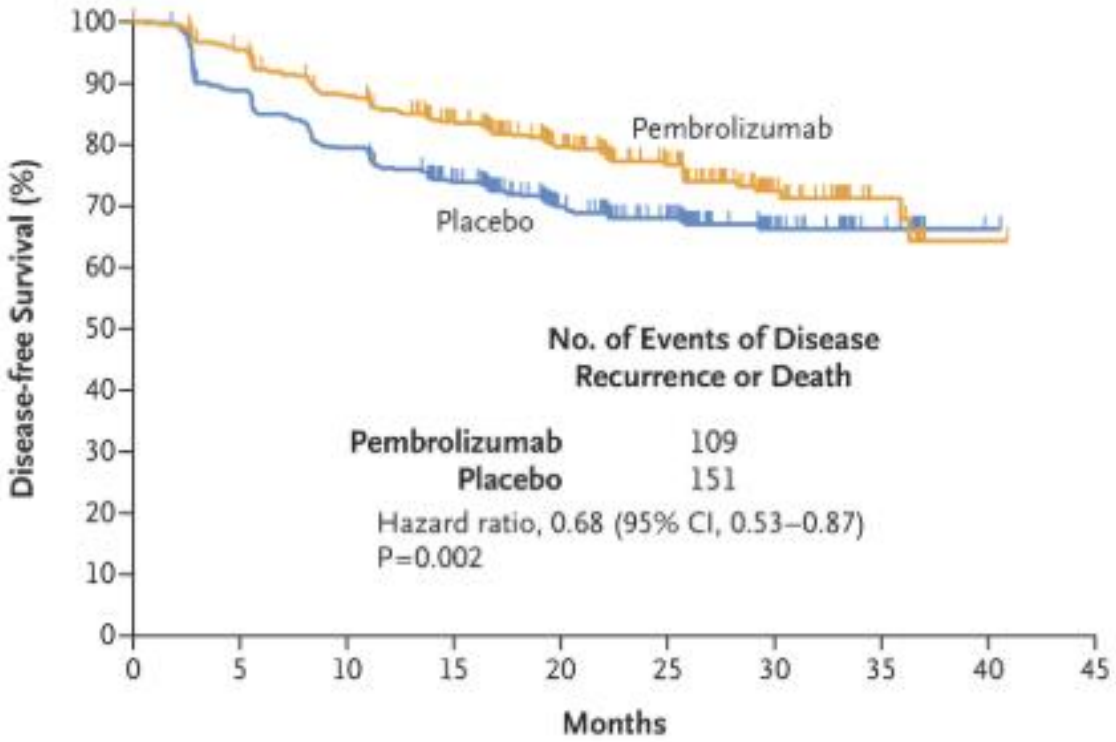
KEYNOTE-564 examined adjuvant pembrolizumab in high risk ccRCC patients



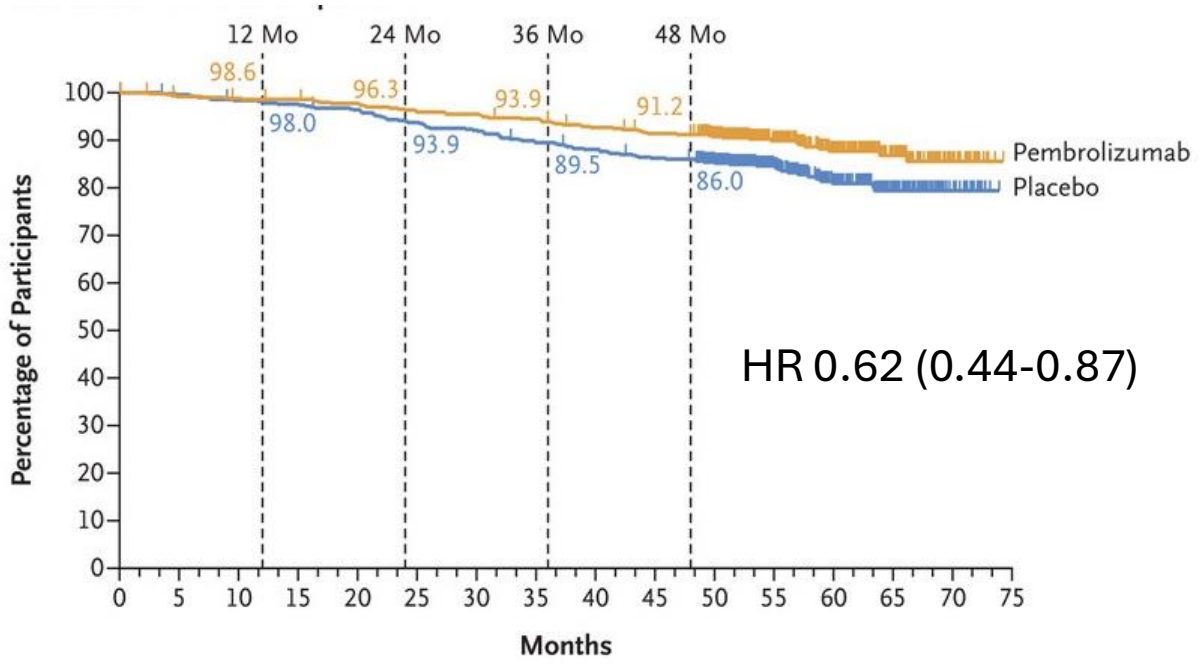
Randomized to 1 year of treatment

- High risk patients
  - Tumor stage 2 with grade 4 or sarcomatoid features
  - Tumor stage 3+
  - Regional LN metastases
  - Stage M1 with NED

Adjuvant pembrolizumab is associated with a benefit in DFS compared with placebo



DFS at 24 months:
- 78% with pembro
- 67% with placebo



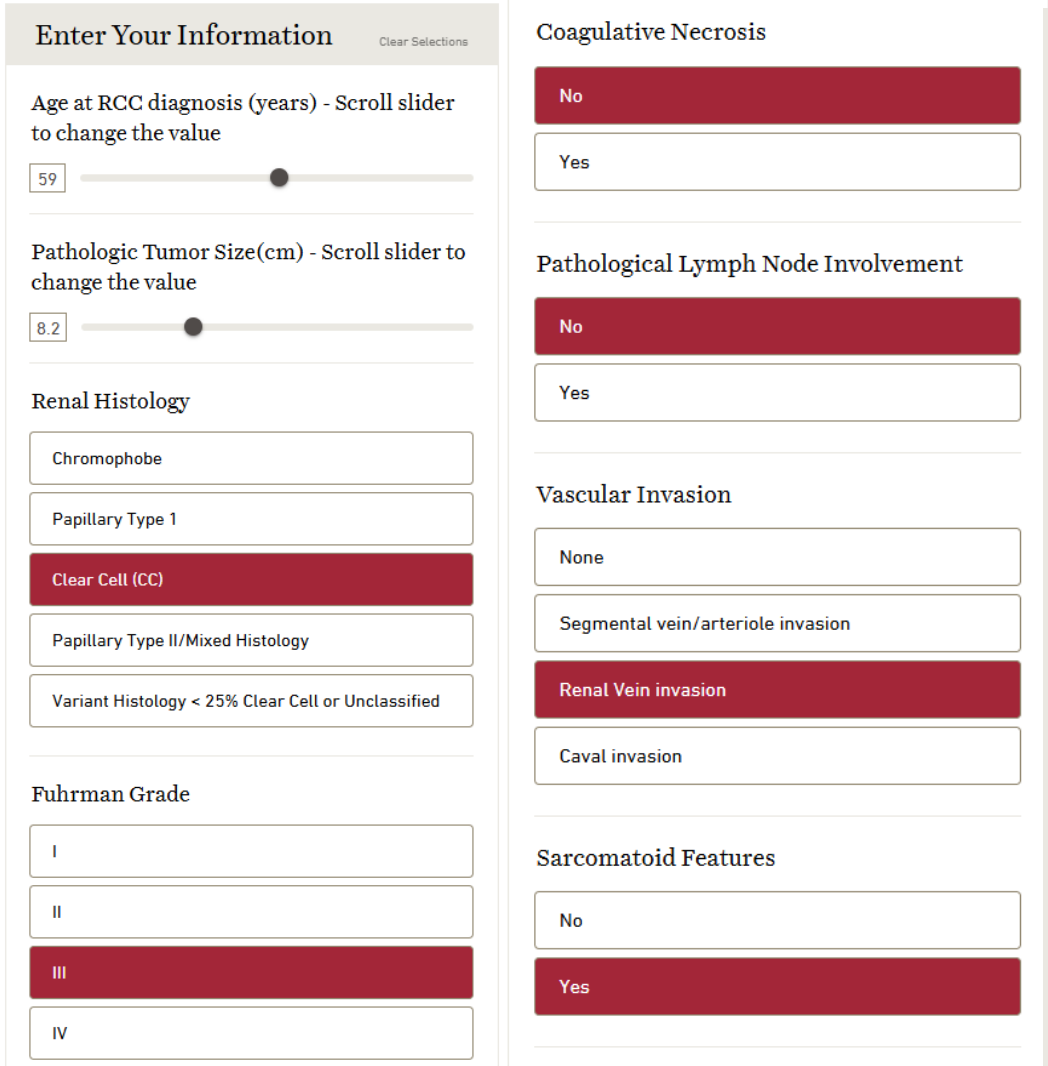
HR 0.62 (0.44-0.87)

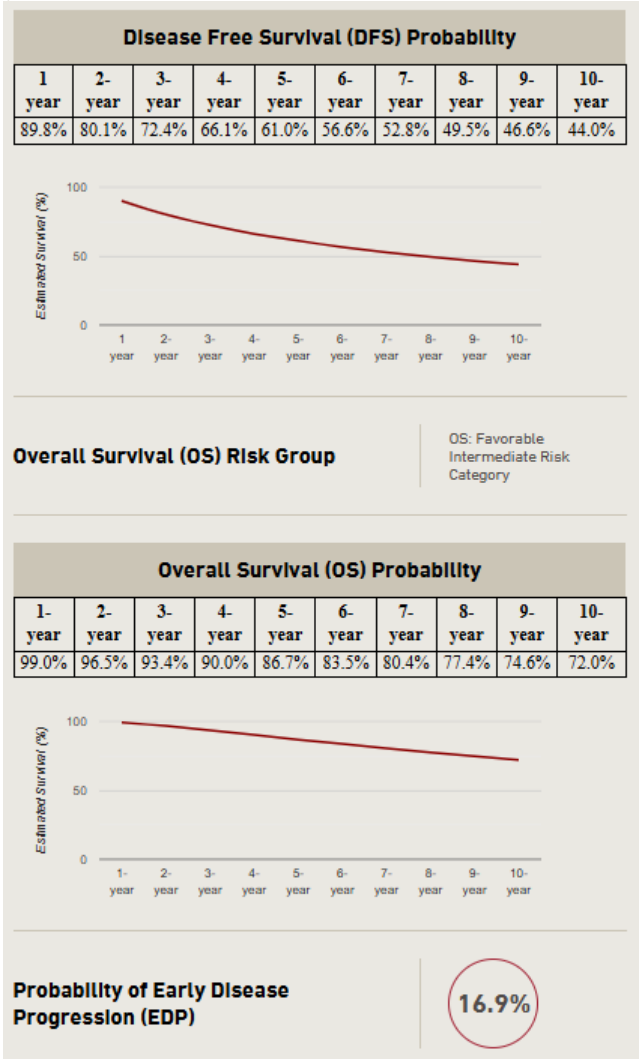
OS at 48 months:
- 91.2% with pembro
- 86% with placebo

Choueiri et al, NEJM 2021. PMID: 34407342
Choueiri et al, NEJM 2024. PMID: 38631003

Nomograms can be used to guide decision making

ASSURE nomogram is an online tool that will provide DFS and OS probabilities based on patient features





https://studies.fccc.edu/nomograms/492

What is the role of immunotherapy and targeted therapy in high risk ccRCC after nephrectomy?

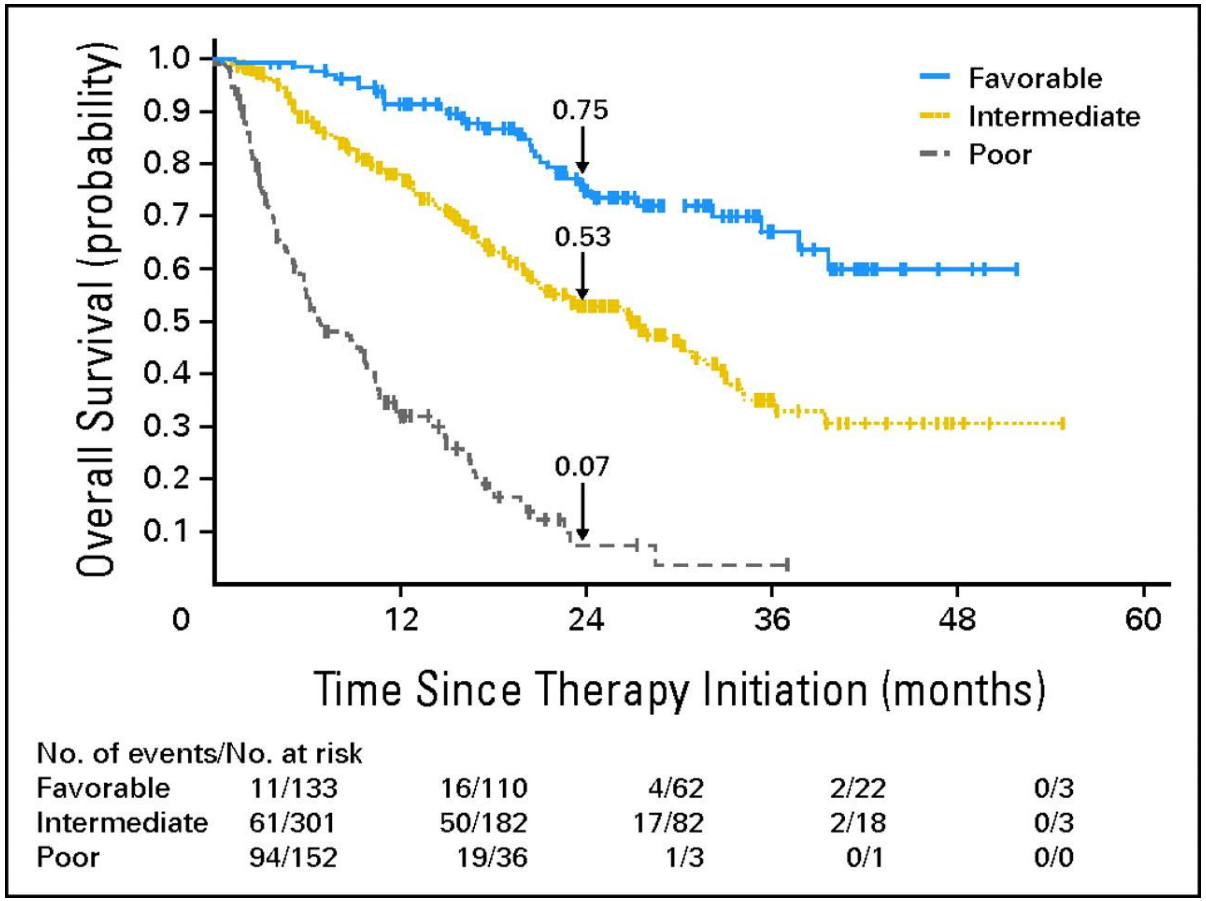
Adjuvant pembrolizumab can be considered for patients with high risk features, such at T2 with grade 4 or sarcomatoid features, T3, T4, regional LN metastases or M1 NED

What is the role of immunotherapy and targeted therapy in Stage IV ccRCC?

IMDC prognostic model estimates disease risk

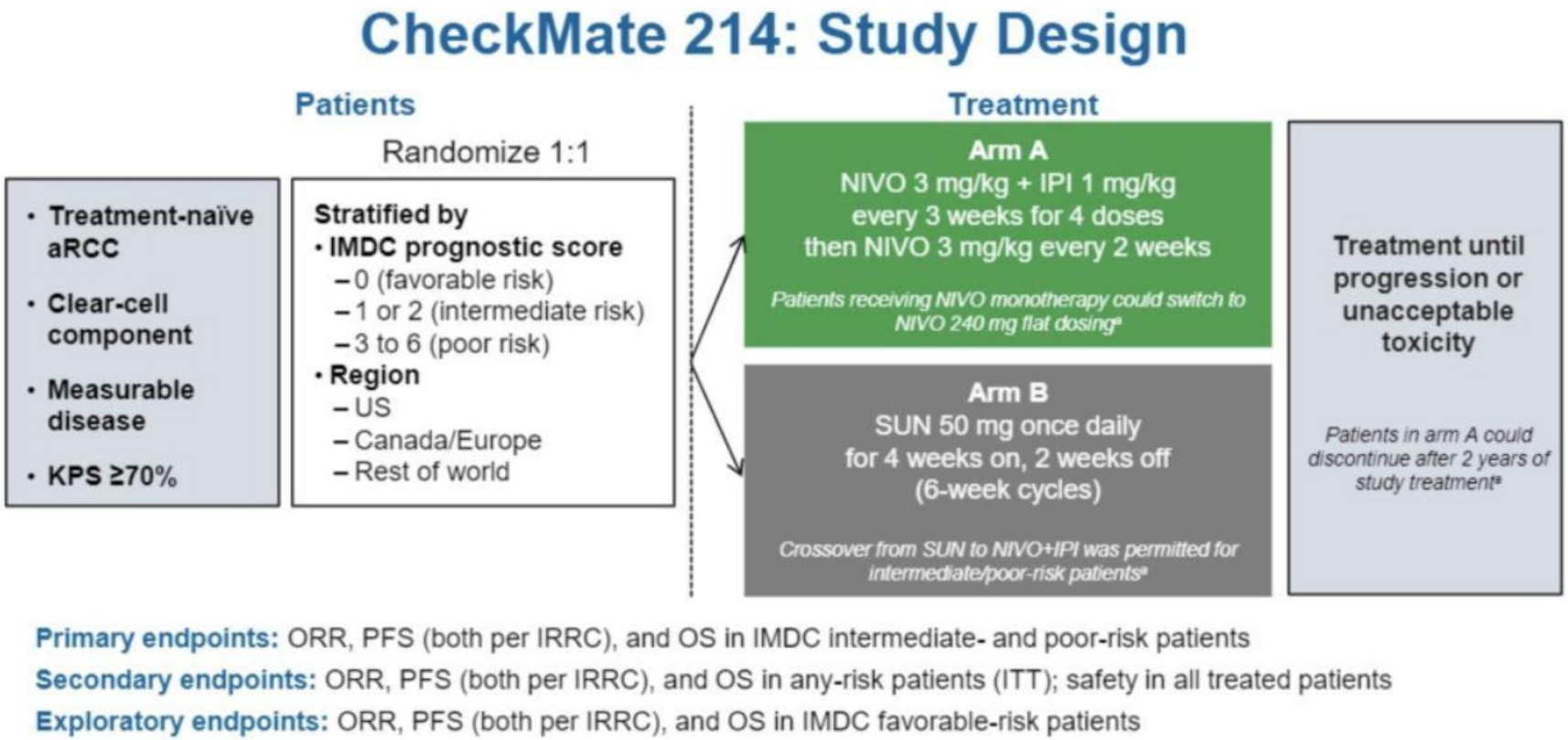
IDMC risk factors
KPS <80%
<1 year from dx to tx
Hgb < LLN
Ca > ULN
ANC > ULN
Plt > ULN

Favorable – 0 risk factors
Intermediate – 1-2 risk factors
Poor – 3+ risk factors

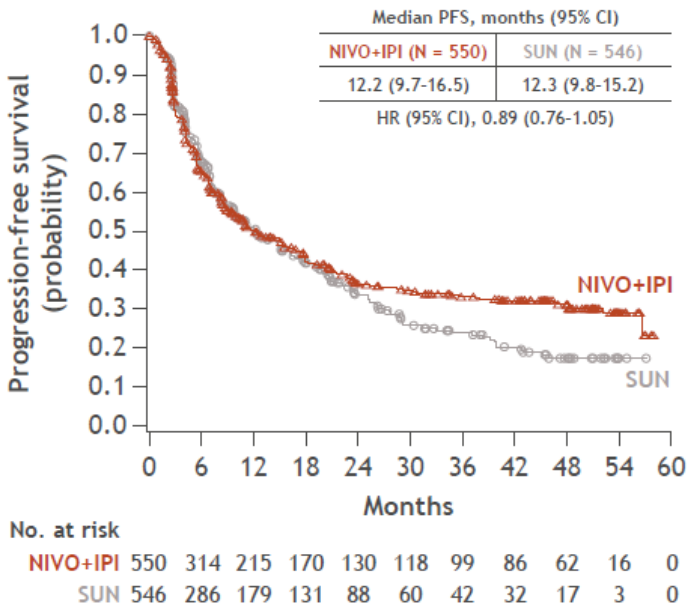


Heng et al, JCO 2009, PMID: 19826129

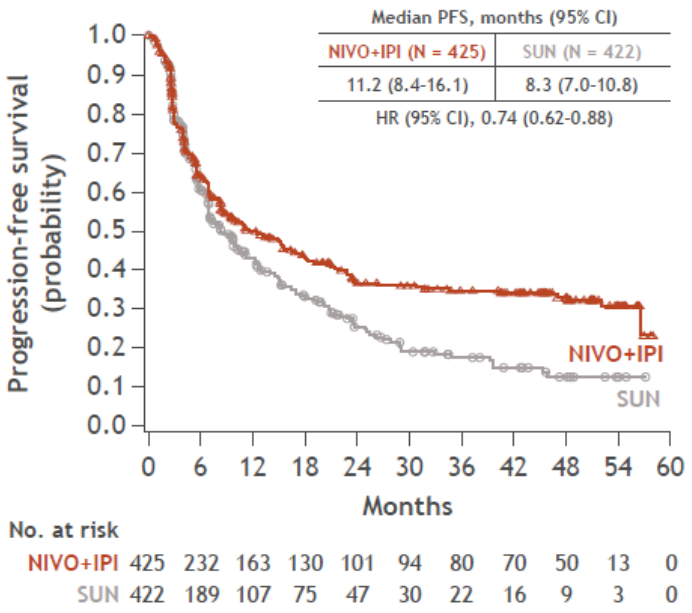
CheckMate 214 studied dual ICI in ccRCC



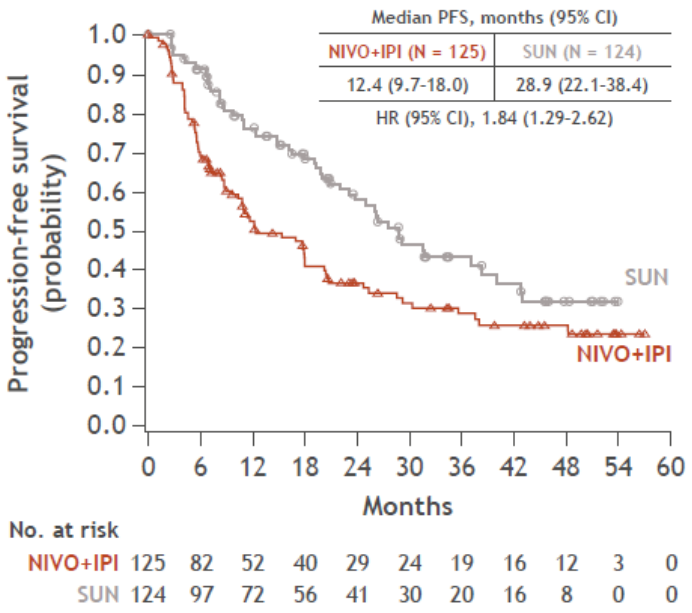
At 48 months, NIVO+IPI showed benefit in intermediate/poor risk populations



ITT population



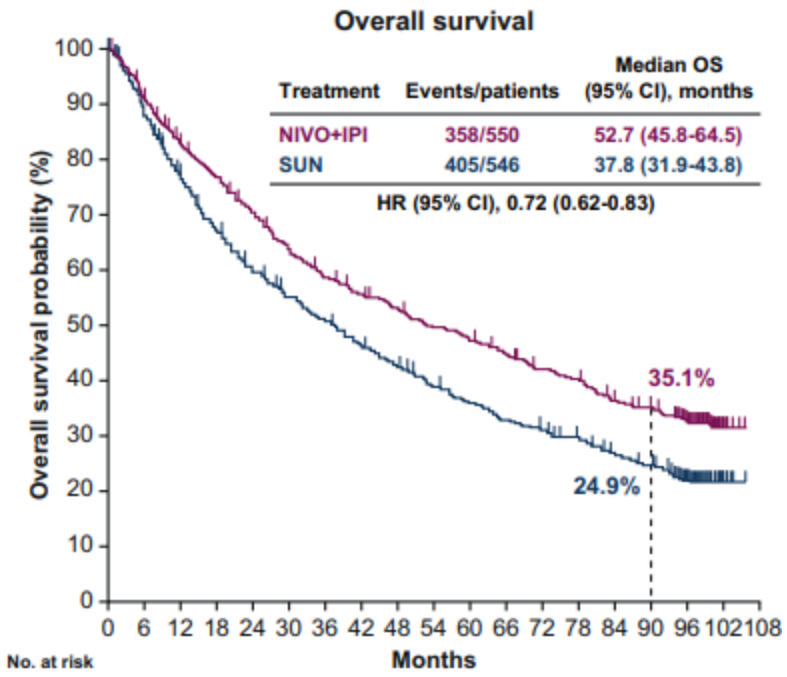
I/P risk population



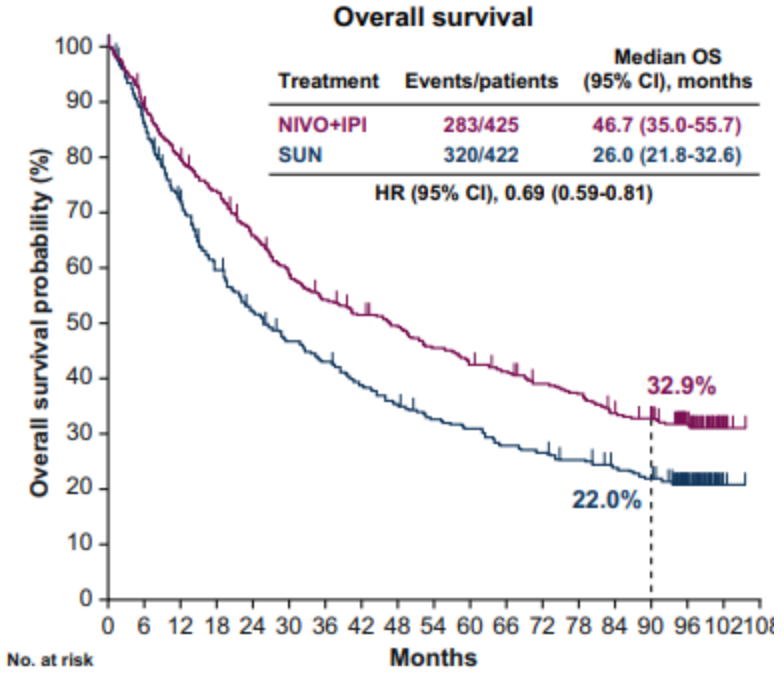
Favorable risk population

Albiges L et al. ESMO 2020. Abstract 711P.

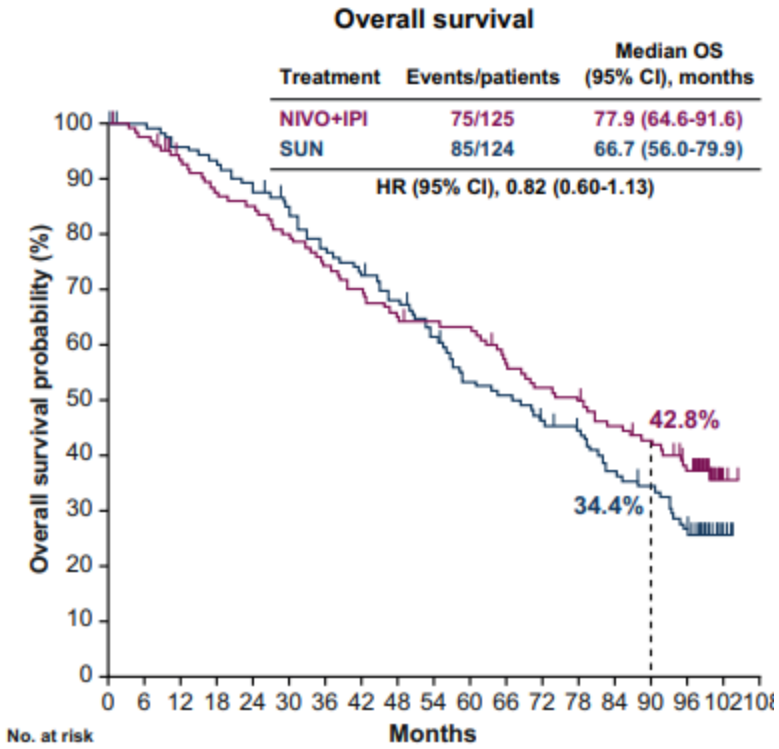
At the 8 year follow up, NIVO+IPI showed benefit in all populations



ITT population



I/P risk population



Favorable risk population

Albiges et al, Ann Oncol 2024. PMID: 39098455

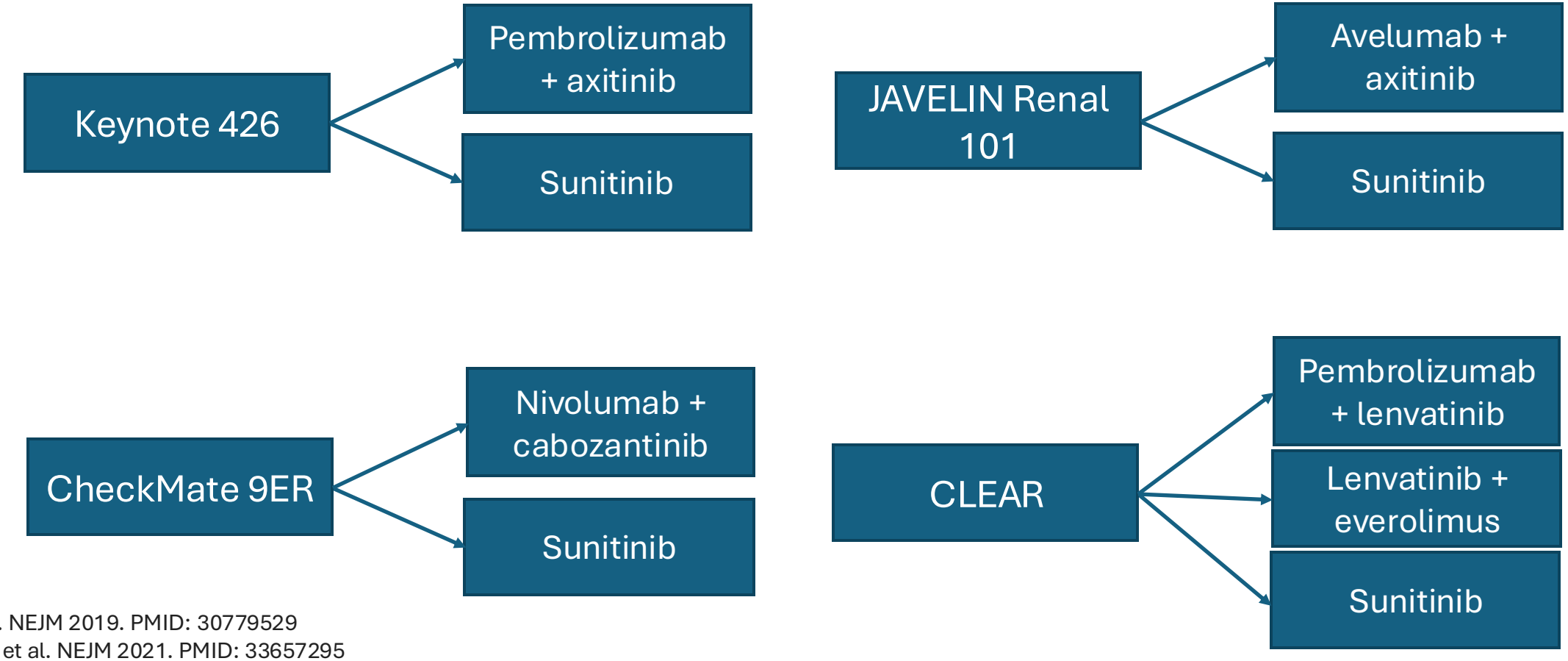
Ipilimumab and Nivolumab in Stage IV ccRCC

- OS benefit in intermediate/poor risk patients at 48 months
- OS benefit in ITT, I/P and favorable populations at 8 years
- 35% OS at 8 years

Event	Nivolumab plus Ipilimumab (N = 547)	
	Any Grade†	Grade 3 or 4
	number of patients (percent)	
All events	509 (93)	250 (46)
Fatigue	202 (37)	23 (4)
Pruritus	154 (28)	3 (<1)
Diarrhea	145 (27)	21 (4)
Rash	118 (22)	8 (1)
Nausea	109 (20)	8 (1)
Increased lipase level	90 (16)	56 (10)
Hypothyroidism	85 (16)	2 (<1)
Decreased appetite	75 (14)	7 (1)
Asthenia	72 (13)	8 (1)
Vomiting	59 (11)	4 (<1)
Anemia	34 (6)	2 (<1)
Dysgeusia	31 (6)	0
Stomatitis	23 (4)	0
Dyspepsia	15 (3)	0
Mucosal inflammation	13 (2)	0
Hypertension	12 (2)	4 (<1)
Palmar–plantar erythrodysesthesia	5 (<1)	0
Thrombocytopenia	2 (<1)	0

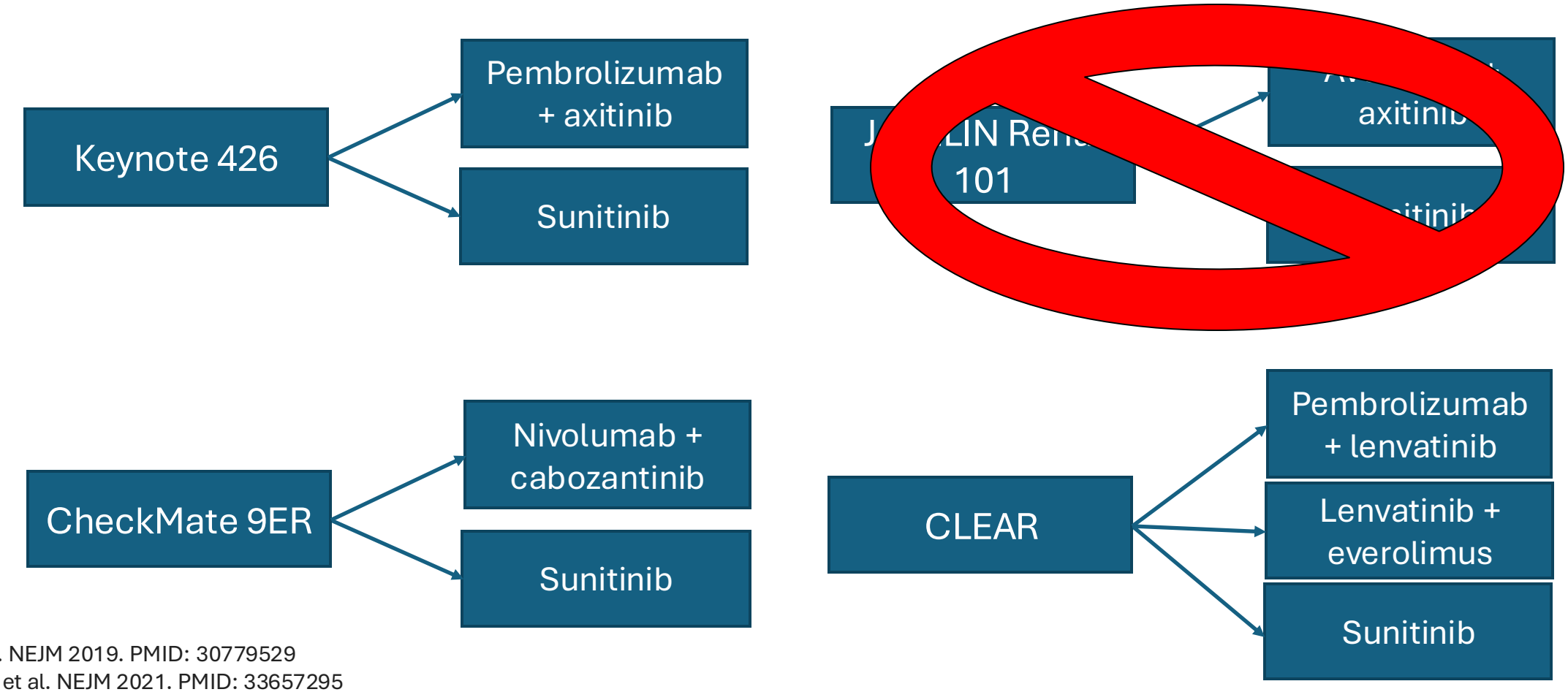
Motzer et al, NEJM 2018. PMID: 29562145

4 combinations of VEGF-targeted therapy + ICI have been studied first line in ccRCC



Rini et al. NEJM 2019. PMID: 30779529
Choueiri et al. NEJM 2021. PMID: 33657295
Motzer et al. JCO 2024. PMID: 38227898
Motzer et al. NEJM 2019. PMID 30779531

3 combinations of VEGF-targeted therapy + ICI are effective first line in ccRCC



Rini et al. NEJM 2019. PMID: 30779529
Choueiri et al. NEJM 2021. PMID: 33657295
Motzer et al. JCO 2024. PMID: 38227898
Motzer et al. NEJM 2019. PMID 30779531

ICI based combinations for Stage IV ccRCC

	CheckMate 214 Ipi/nivo v sunitinib	KEYNOTE-426 Pembro+axi v sunitinib	CheckMate 9ER Nivo+cabo v sunitinib	CLEAR Pembro+lenva v sunitinib
mPFS (months) HR	**12.2** vs 12.3 0.89 (0.76–1.05)	**15.7** vs 11.1 0.68 (0.58–0.80)	**17.0** vs 8.3 0.52 (0.43–0.64)	**23.9** vs 9.2 0.39 (0.32-0.49)
mOS (months) HR	**52.7** v 37.8 **0.73** (0.60-0.88)	NR vs 29.5 **0.66** (0.50–0.87)	NR vs NR **0.66** (0.49-0.88)	45.7 vs 40.1 **0.73** (0.60-0.88)
ORR (%)	**39.5** vs 33	**60** vs 40	**55** vs 27	**71** vs 36
CR (%)	**12** vs 3.5	**10** vs 4	**9** vs 4	**16** vs 4
Prognostic Risk % Favorable Intermediate Poor	 23 61 17	 32 55 13	 23 58 19	 31 59 9
>= Grade 3 TRAE	46 vs 63	68 vs 64	61 vs 51	72 vs 59
	PMID: 29562145	PMID: 30779529	PMID: 33657295	PMID: 38227898

NCCN guidelines include ICI/ICI and ICI/TKI

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Kidney Cancer

PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV (M1 OR UNRESECTABLE T4, M0) OR RELAPSED 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,c] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Ipilimumab + nivolumab[b,d]	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Pazopanib • Sunitinib	• Active surveillance[1,2,3] • Axitinib (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b,c] (category 1) • Ipilimumab + nivolumab[b,d] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B)

NCCN.org

Dual ICI vs ICI-TKI Combination

	Pros	Cons
ICI/ICI	• Durable responses • Treatment-free interval possible • OS advantage over TKI monotherapy	• Potential long-term toxicity • Lower ORR
ICI/TKI	• Higher ORR • Rapid responses • Dose adjustment possible	• Lack of durable response • Acute toxicity • Pill burden

ICI/TKI combinations have varying schedules and pharmacologic properties

	Keynote 426 Pembrolizumab + Axitinib	Checkmate 9ER Nivolumab + Cabozantinib	CLEAR Pembrolizumab + Lenvatinib
TKI half-life	2.5-6.1 hrs	120 hrs	28 hrs
TKI dosing interval	BID	Daily	Daily
IO dosing interval	Q3weeks (/q6w)	Q2weeks (/q4w)	Q3weeks (/q6w)
Hold TKI before surgery interval	24-48 hrs	28 days	7 days

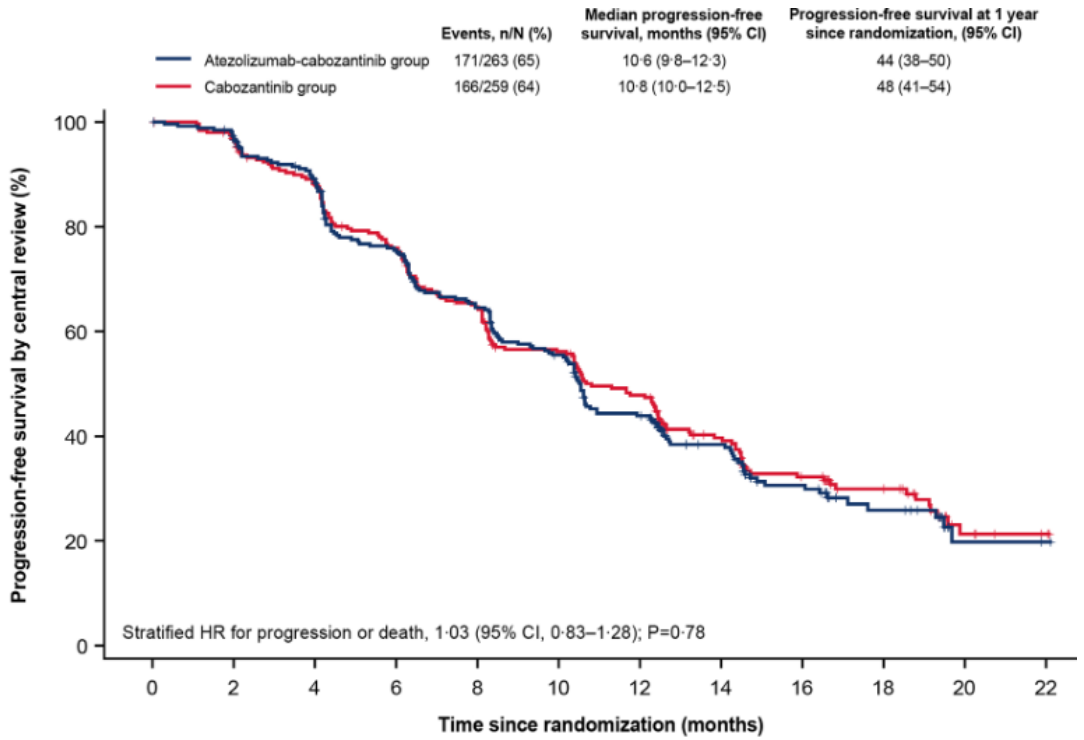
Rini et al. NEJM 2019. PMID: 30779529
Choueiri et al. NEJM 2021. PMID: 33657295
Motzer et al. JCO 2024. PMID: 38227898

What is the role of immunotherapy and targeted therapy in Stage IV ccRCC?

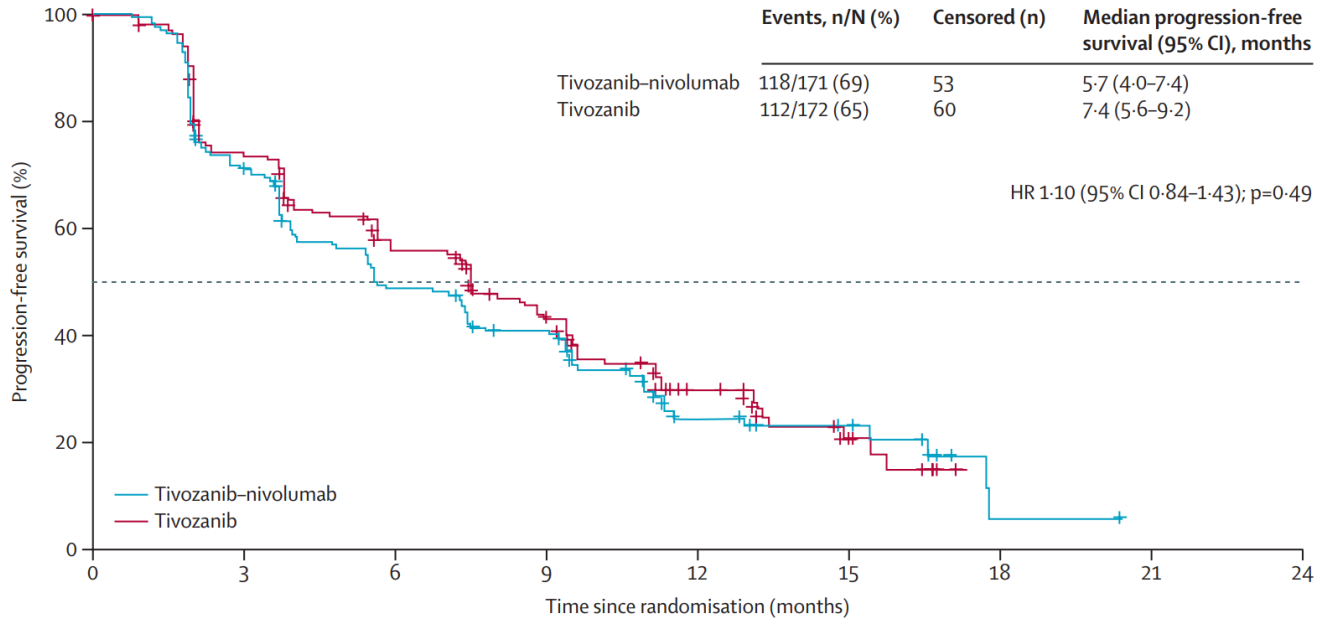
First line therapy is based in immune checkpoint inhibitors, either in combination with TKI or in ICI doublet therapy

What is the role of immunotherapy and targeted therapy in Stage IV ccRCC that has progressed on treatment?

ICI is not effective after progression on prior ICI



CONTACT-03 – Atezolizumab+cabozantinib v cabozantinib



TiNivo-2 – Tivozanib+nivolumab v tivozanib

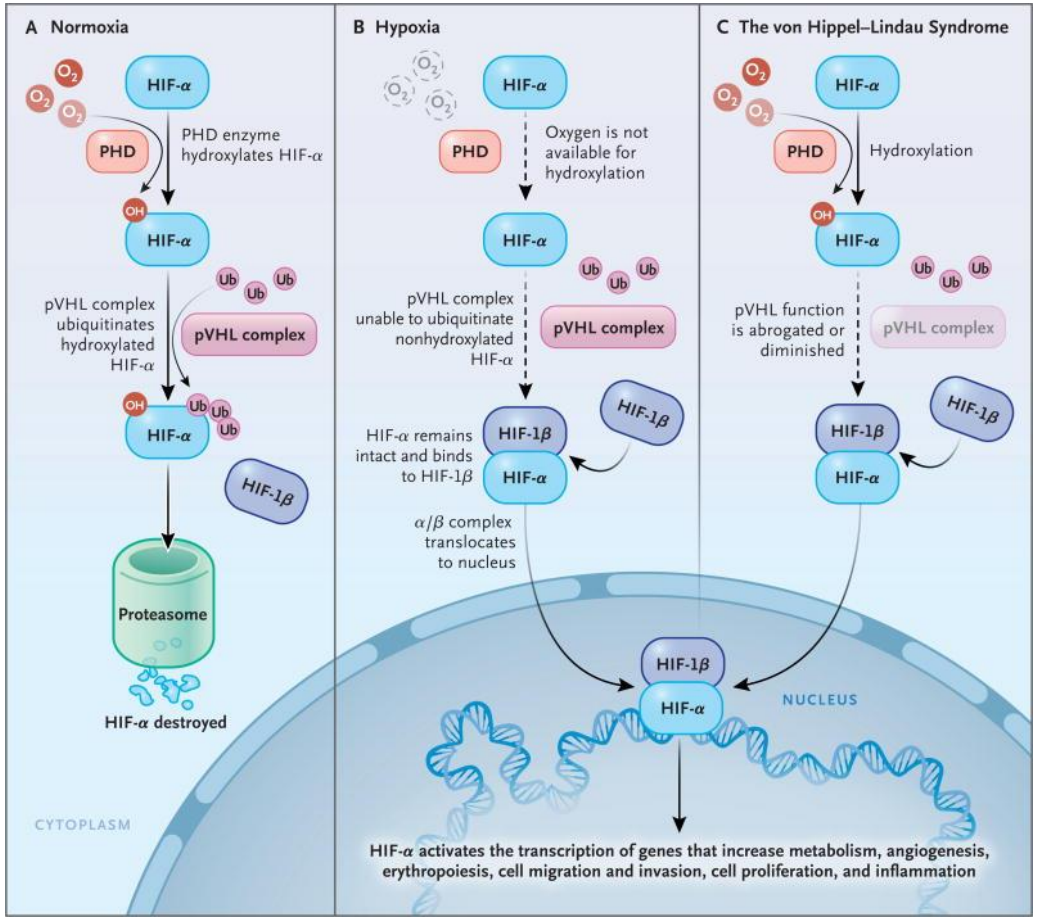
Pal et al, Lancet 2023. PMID: 37290461
Choueiri et al, Lancet 2024. PMID: 37290461

Additional studies are needed in the ICI refractory setting

Previous treatment	TKI		ICI			
Trial	METEOR[3]	Lenvatinib phase 2[4]	Axitinib phase 2[5]	CaboPoint[6]	KEYNOTE-146[7]	CONTACT-03[8]
Treatment	Cabozantinib	Lenvatinib plus everolimus	Axitinib	Cabozantinib	Lenvatinib plus pembrolizumab	Cabozantinib plus atezolizumab
Comparison	Everolimus	Lenvatinib or everolimus	None	None	None	Cabozantinib
Number of patients	330 / 328	51 / 50 / 52	40	31	104	259 / 254
ORR (%)	17 / 3	43 / 27 / 6	45	37.9	62.5	41 / 41
PFS (months)	7.4 / 3.9	14.6 / 7.4 / 5.5	8.8	NA	11.8	10.6 / 10.8

Fahey, Rini, Beckerman, ASCO Daily News 11/29/2023

Belzutifan is a HIF-2 targeted agent with activity in refractory RCC



- VHL is lost in 90% of ccRCC tumors
- VHL loss leads to increased levels of HIF transcription factors
- HIF activity drives expression of genes involved in hypoxia, metabolism, angiogenesis

Simon. NEJM 2016. PMID: 27618882

Belzutifan is a HIF-2 targeted agent with activity in refractory RCC

Key Eligibility Criteria

- Unresectable, locally advanced or metastatic clear cell RCC
- Disease progression after 1-3 prior systemic regimens, including ≥1 anti–PD-(L)1 mAb and ≥1 VEGFR-TKI
- Karnofsky Performance Status score ≥70%

R 1:1

N = 374 → **Belzutifan** 120 mg orally daily

N = 372 → **Everolimus** 10 mg orally daily

Stratification Factors

- IMDC prognostic score[a]: 0 vs 1-2 vs 3-6
- Prior VEGFR-targeted therapies: 1 vs 2-3

Dual Primary Endpoints:

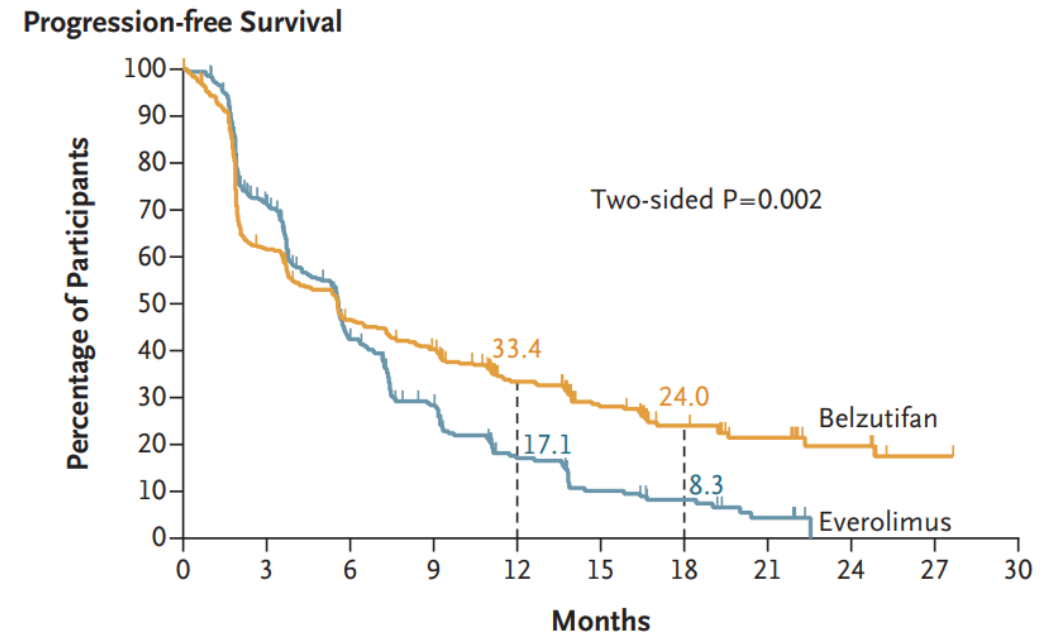
- PFS per RECIST 1.1 by BICR
- OS
- The study was considered positive if either of the dual primary endpoints was met

Key Secondary Endpoint:

- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:

- DOR per RECIST 1.1 by BICR
- Safety



No. at Risk

Belzutifan	374	218	157	134	85	55	32	20	11	1	0
Everolimus	372	226	113	68	31	17	10	4	0	0	0

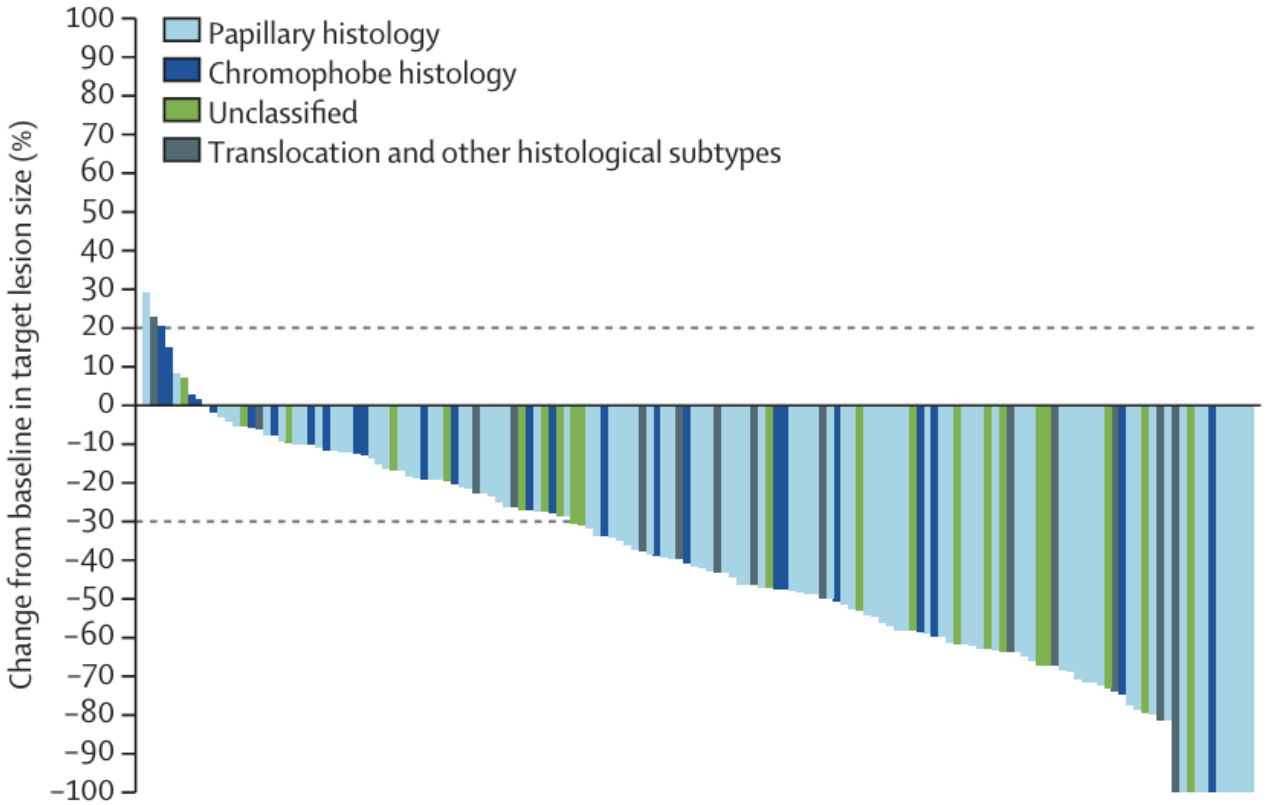
Choueiri et al, NEJM 2024. PMID: 39167807

What is the role of immunotherapy and targeted therapy in Stage IV ccRCC that has progressed on treatment?

ICI should not be continued in patients who have received prior ICI
VEGFR-TKI and HIF inhibitors can be considered in this setting

What is the role of immunotherapy and targeted therapy in Stage IV non-ccRCC?

Pembrolizumab plus lenvatinib has activity in non-clear cell mRCC



- 158 pts with non-ccRCC
- ORR 49% (6% CR)
- mPFS 18 months
- 12 mo OS 82%

Albiges et al, Lancet Oncol 2023. PMID 37451291

Additional studies have examined ICI combinations in nccRCC

Trial/Treatment	ORR	Best response = PD	mDOR	mPFS	mOS
Keynote-B61 (1L) Pembrolizumab + Lenvatinib (n=158)	49% ORR 6% CR	11%	NR (75% at 12mos)	18 months (63% at 12 mos)	NR (82% at 12 mos)
Lee et al (1 or 2L) Nivolumab + cabozantinib (n=40)	48% ORR	4%	17 mos (~65% at 12mos)	13 months (51% at 12 mos)	28 mos (70% at 18 mos)
SUNNIFORECAST (1L) Ipilimumab + nivolumab (n= 156)	33% ORR	34%	?	5.5 months	42 mos (87% at 12 mos)
SUNNIFORECAST (1L) SOC (n= 143) (mostly TKI)	20% ORR	19%	?	5.7 months	34 mos (77% at 12 mos)

Albiges et al, Lancet Oncol 2023. PMID 37451291
Lee et al, JCO 2022. PMID 35298296
Bergmann et al, ESMO Congress 2024 abstract LBA75

Take Home Points

- Adjuvant pembrolizumab can be considered for patients with high risk ccRCC
- Frontline therapy for metastatic ccRCC is ICI based, with either ICI doublet therapy or ICI+VEGFR-TKI being standard of care
- ICI should not be continued after initial progression on ICI
- ICI treatments are less well studied in nccRCC however multiple trials have shown response for both ICI doublet and ICI+VEGFR-TKI
- Novel HIF targeting belzutifan can be considered on progression