2023 ASCO® ANNUAL MEETING

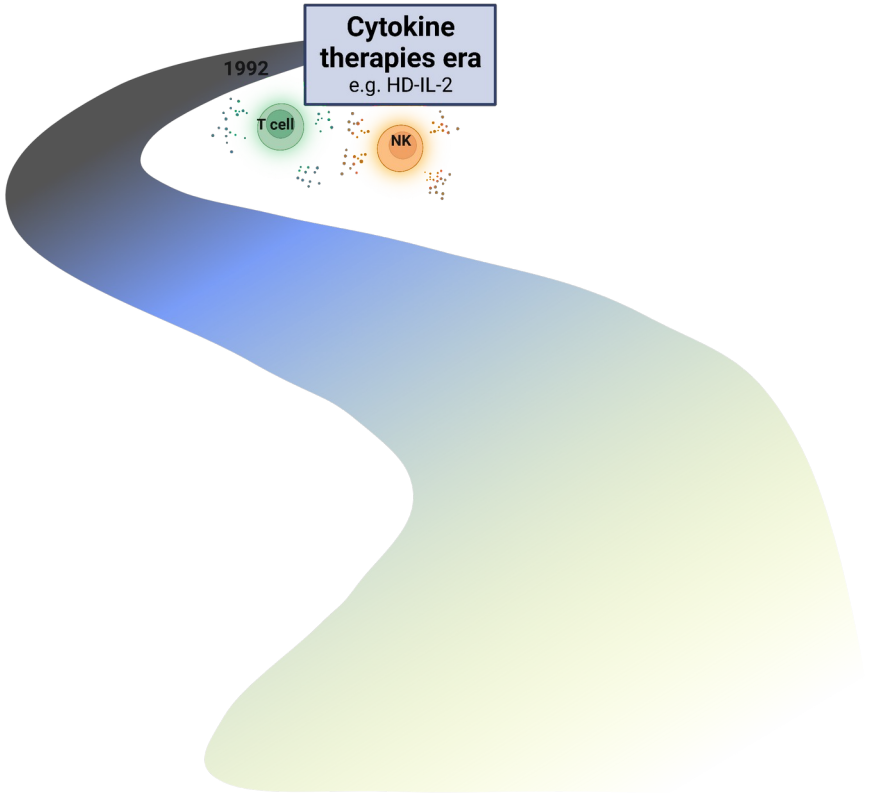
Combination Therapies Come of Age in Kidney Cancer

Discussion of abstracts LBA4500, LBA4501, and 4502

David A. Braun, MD, PhD

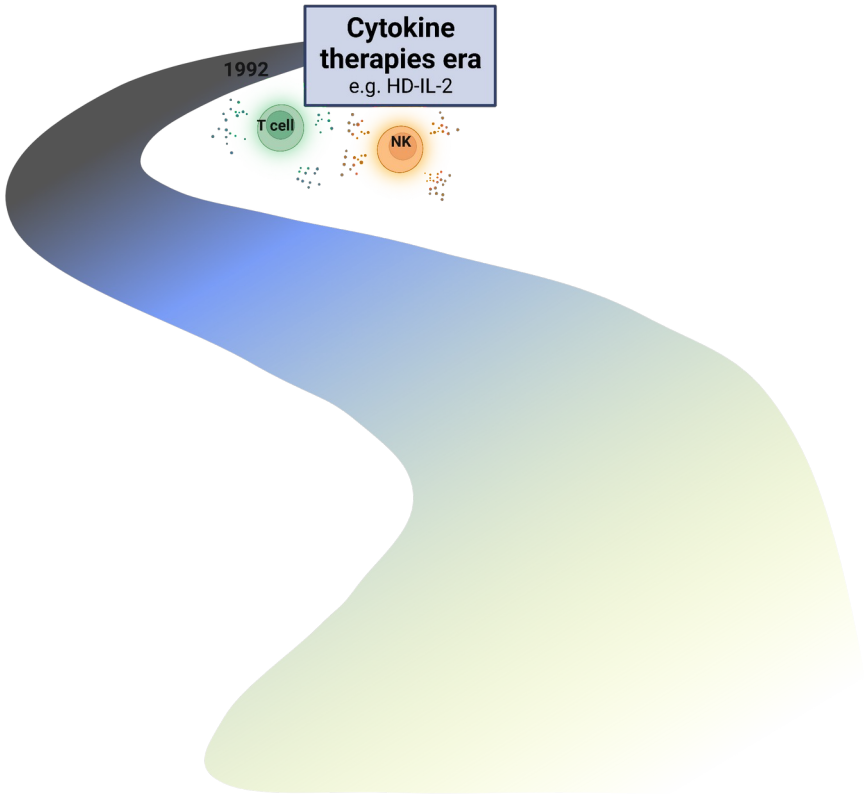
Yale Cancer Center | Yale School of Medicine

Evolving landscape of systemic therapies for RCC



Kashima & Braun, Urol Clin N Am, 2023.

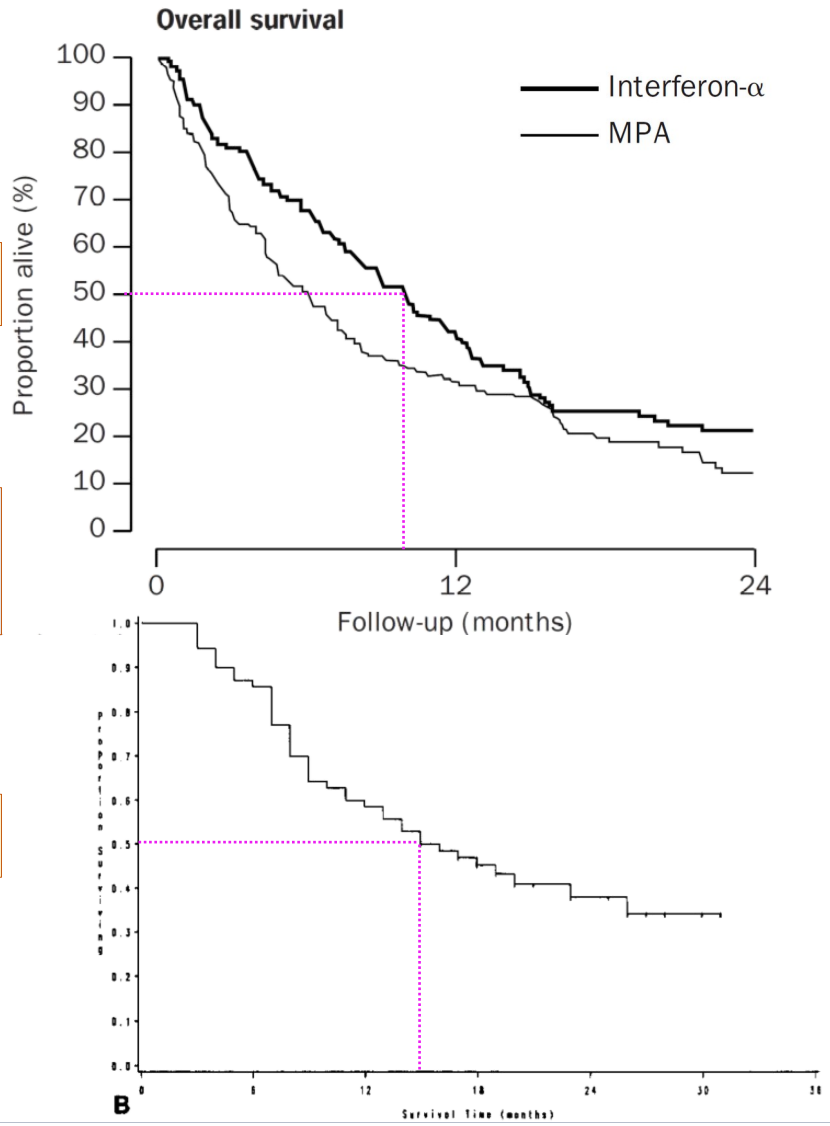
Evolving landscape of systemic therapies for RCC



IFNα

Median OS ~ 1 year

IL-2



Kashima & Braun, Urol Clin N Am, 2023; MRC Renal cell Collaborators, Lancet, 1998; Atkins, J Clin Oncol, 1995.

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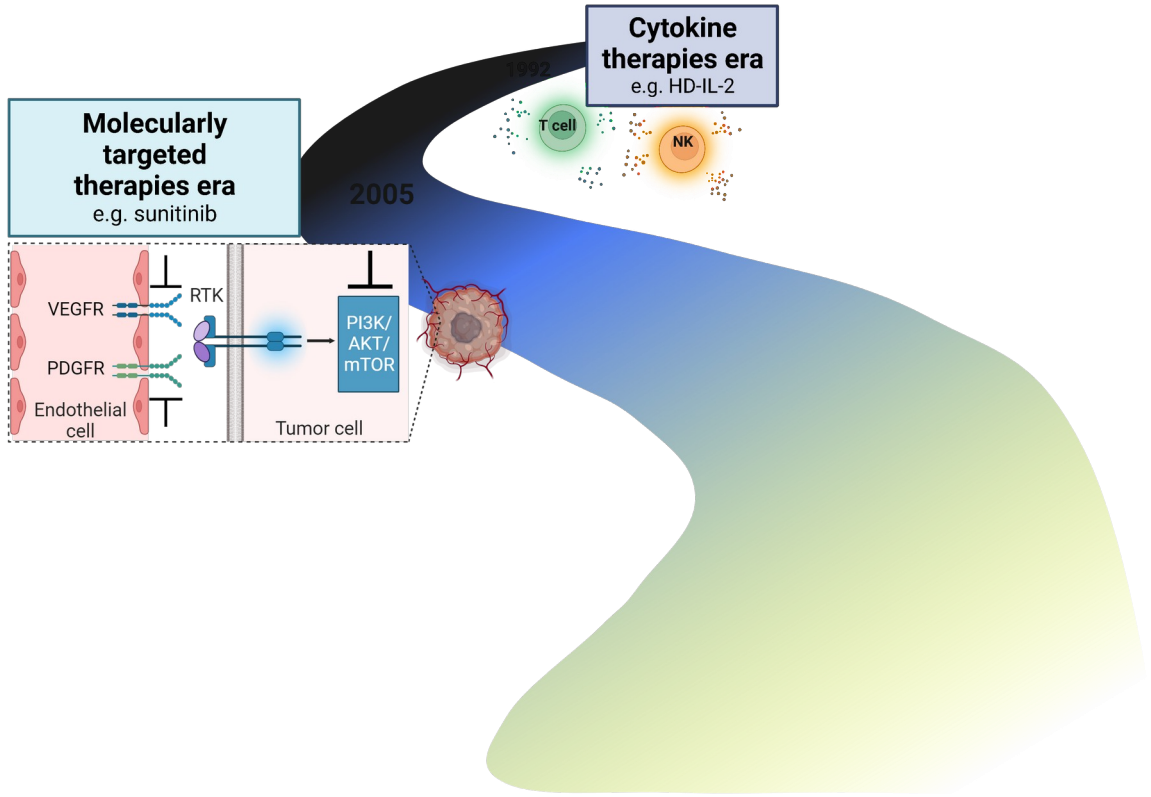
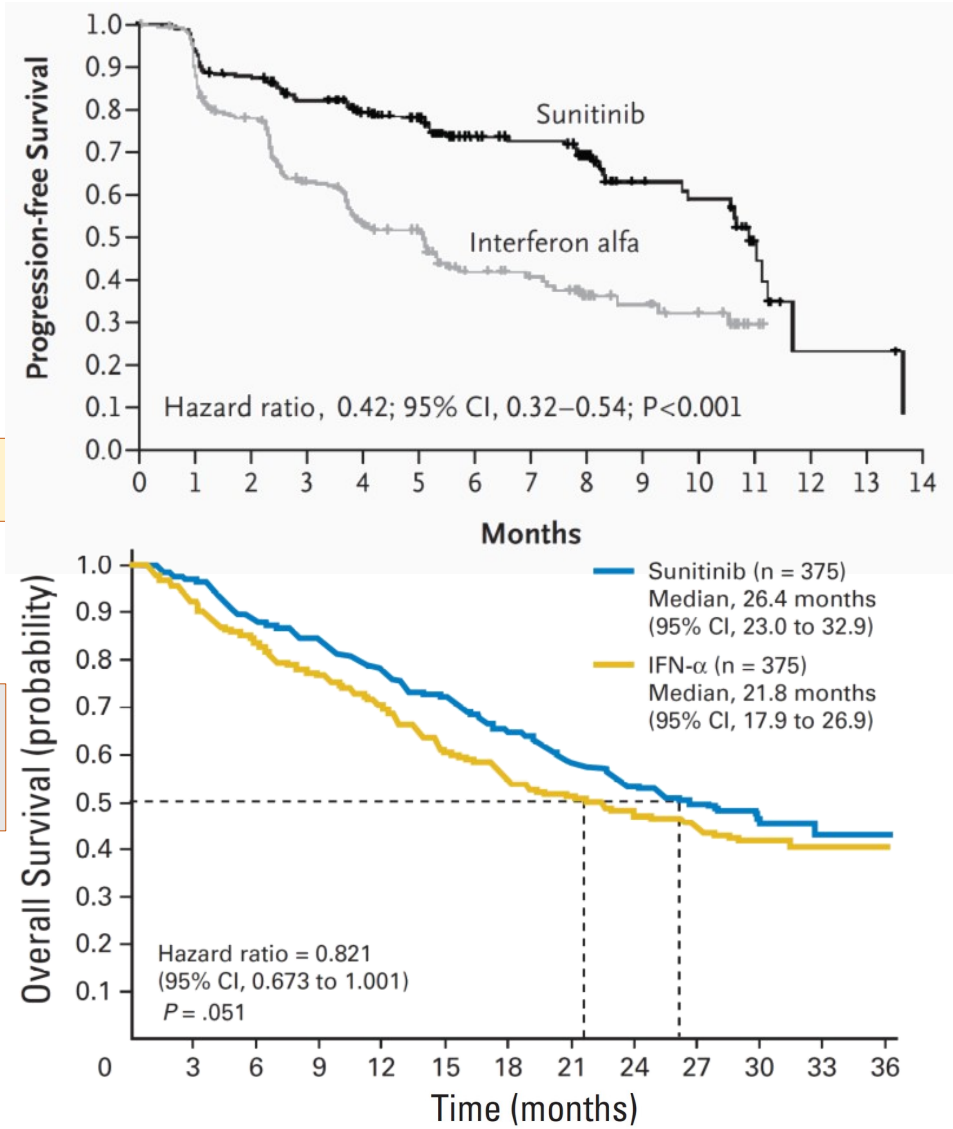


Sunitinib

Median OS ~ 2 years



Kashima & Braun, Urol Clin N Am, 2023; Motzer, N Engl J Med, 2007; Motzer, J Clin Oncol, 2009.

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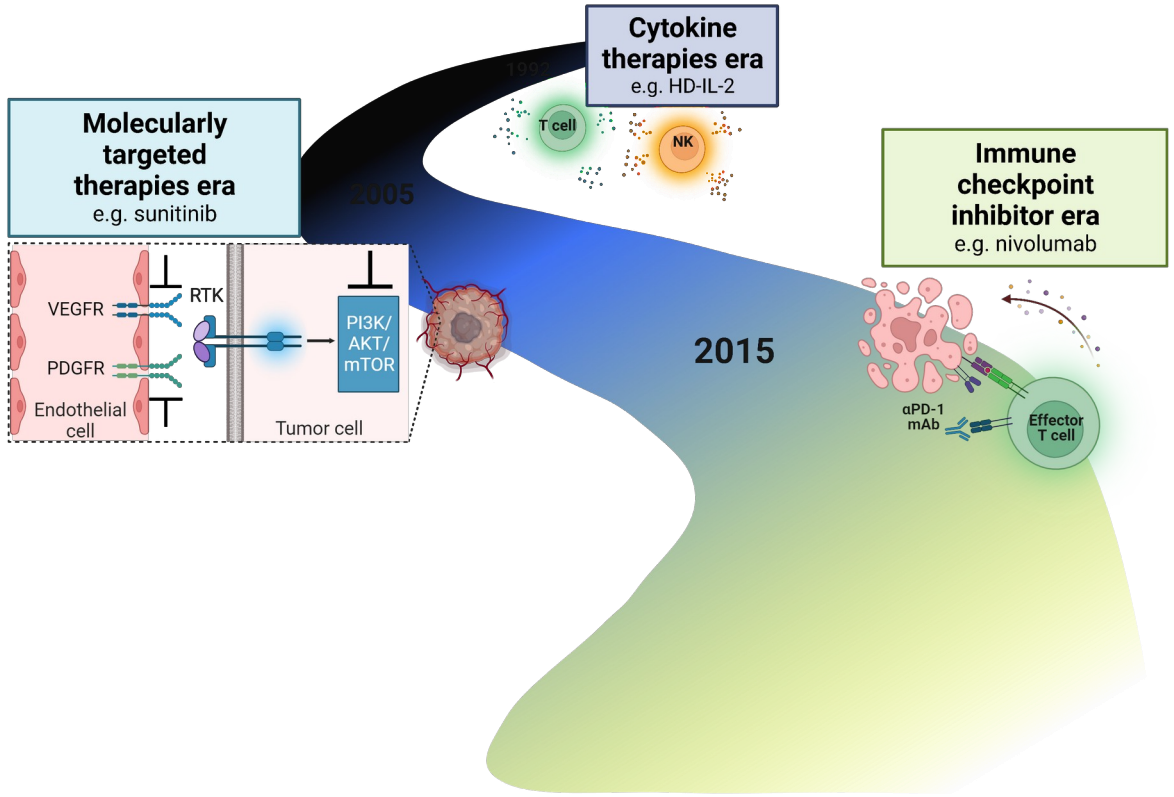
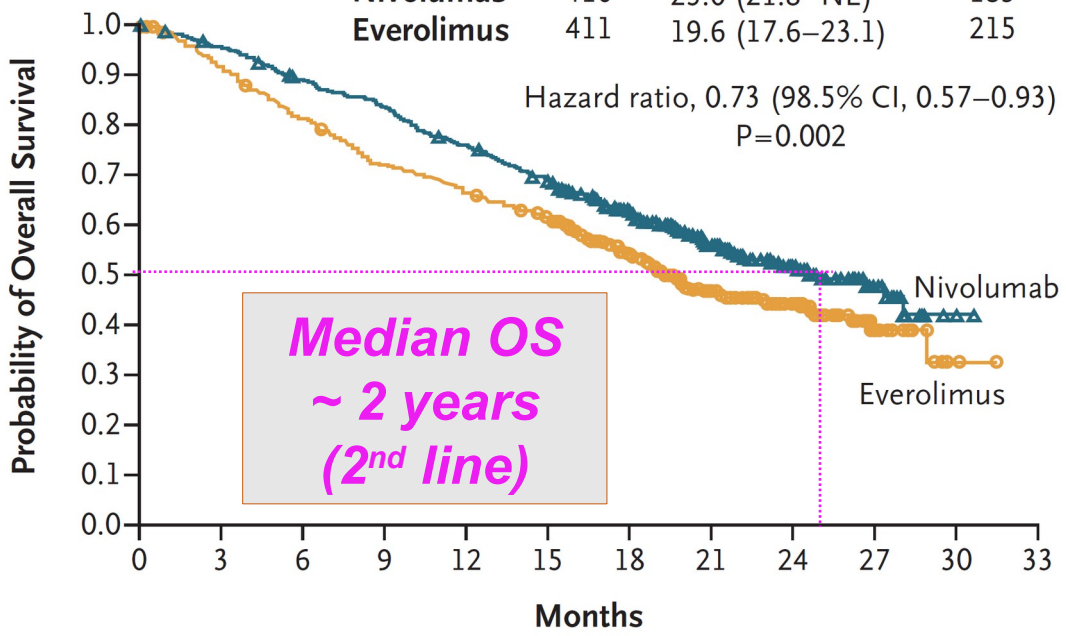


Nivolumab

	No. of Patients	Median Overall Survival (95% CI)	No. of Deaths
		mo	
Nivolumab	410	25.0 (21.8–NE)	183
Everolimus	411	19.6 (17.6–23.1)	215

Hazard ratio, 0.73 (98.5% CI, 0.57–0.93)
P=0.002



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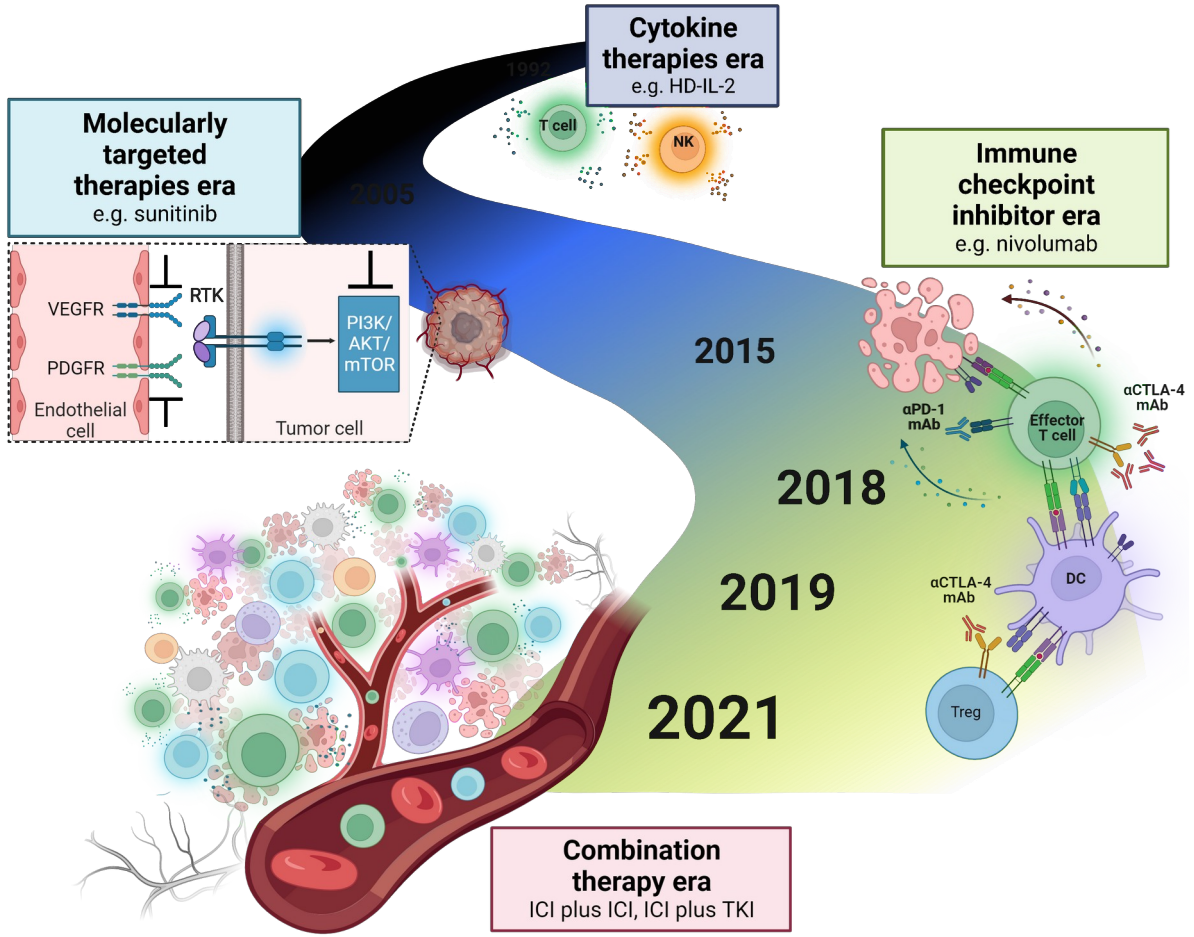
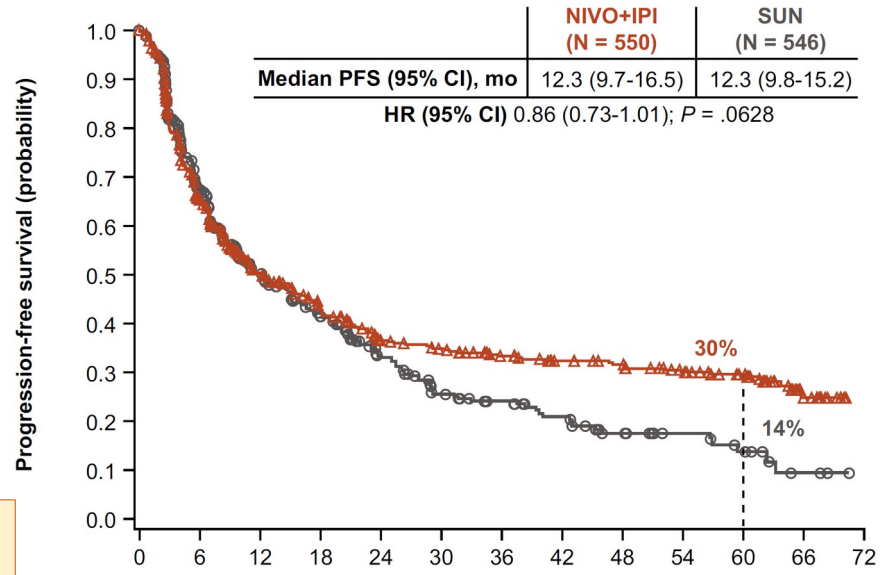
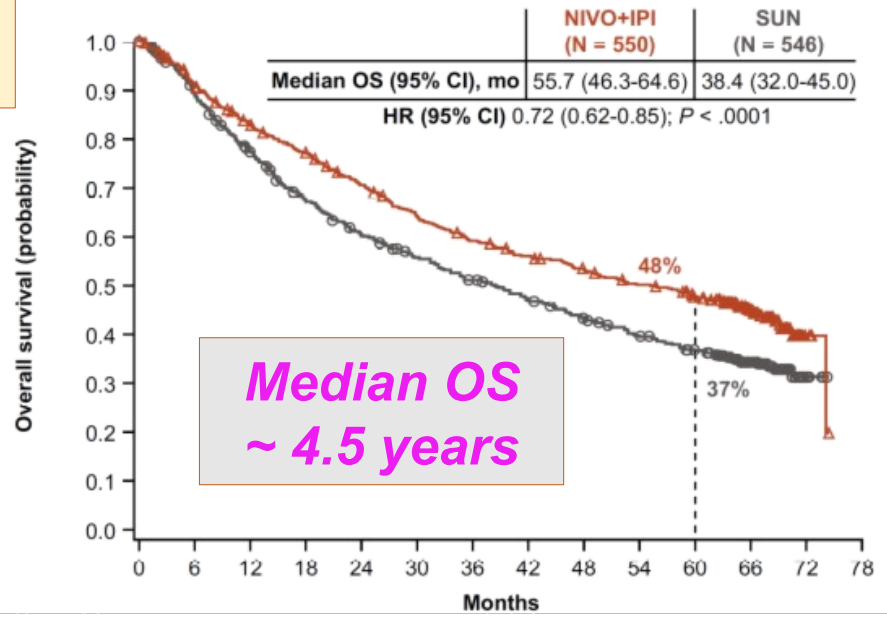


Kashima & Braun, Urol Clin N Am, 2023; Motzer, Cancer, 2022.

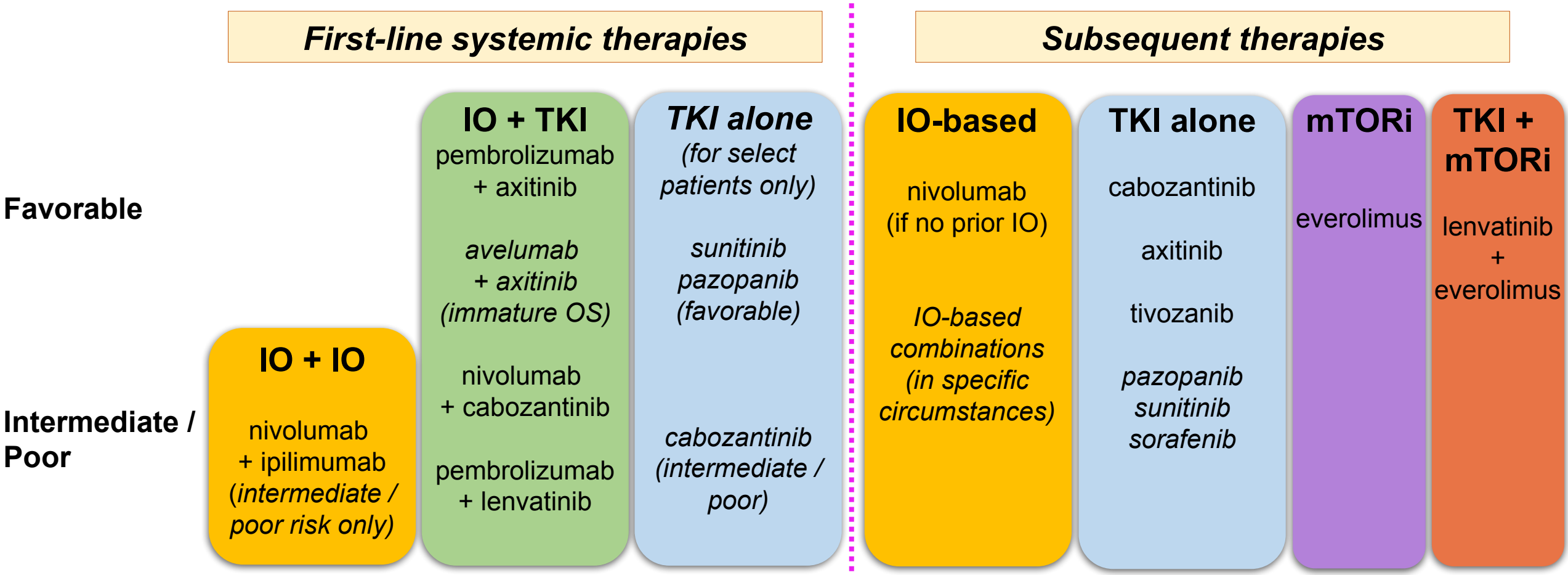
Nivolumab + Ipilimumab



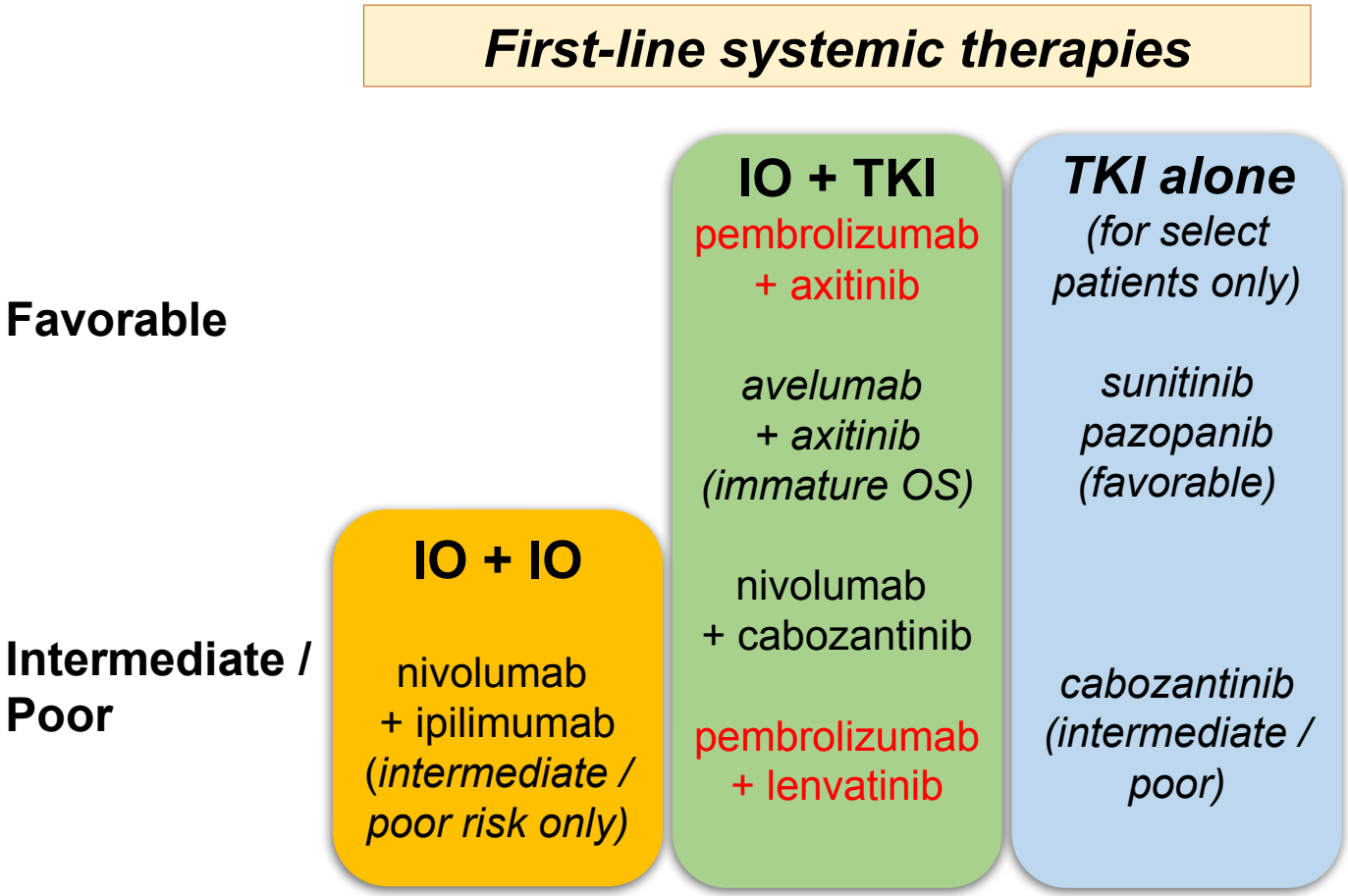


Median OS ~ 4.5 years

Systemic therapies for clear cell RCC



Discussion for oral abstract session: genitourinary cancer – kidney and bladder



Abstract LBA4501 (Rini):

Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: 5-year analysis of KEYNOTE-426.

Abstract 4502 (Hutson):

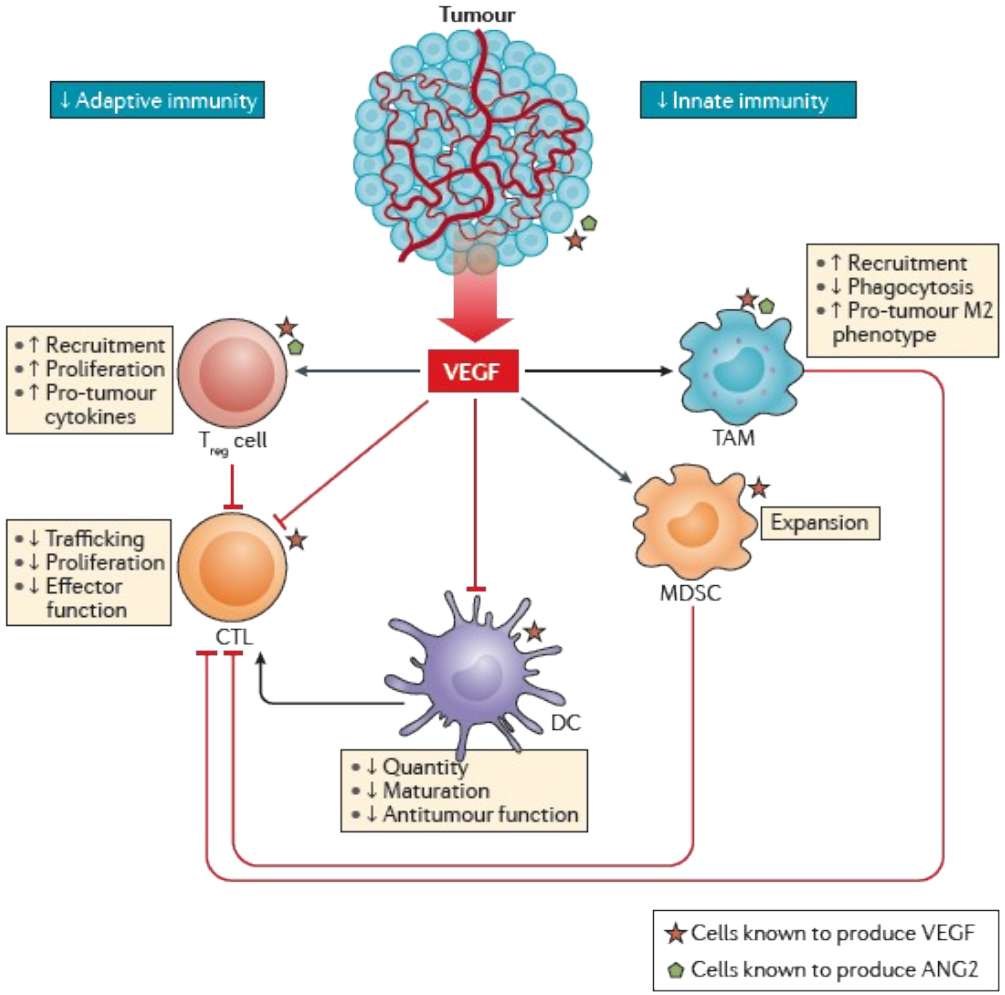
Final prespecified overall survival (OS) analysis of CLEAR: 4-year follow-up of lenvatinib plus pembrolizumab (L+P) vs sunitinib (S) in patients (pts) with advanced renal cell carcinoma (aRCC).

IO+VEGF TKI: biological rationale

VEGF TKIs: T cells

↓ T_{regs}

↑ *effector CTL*



VEGF TKIs: myeloid cells

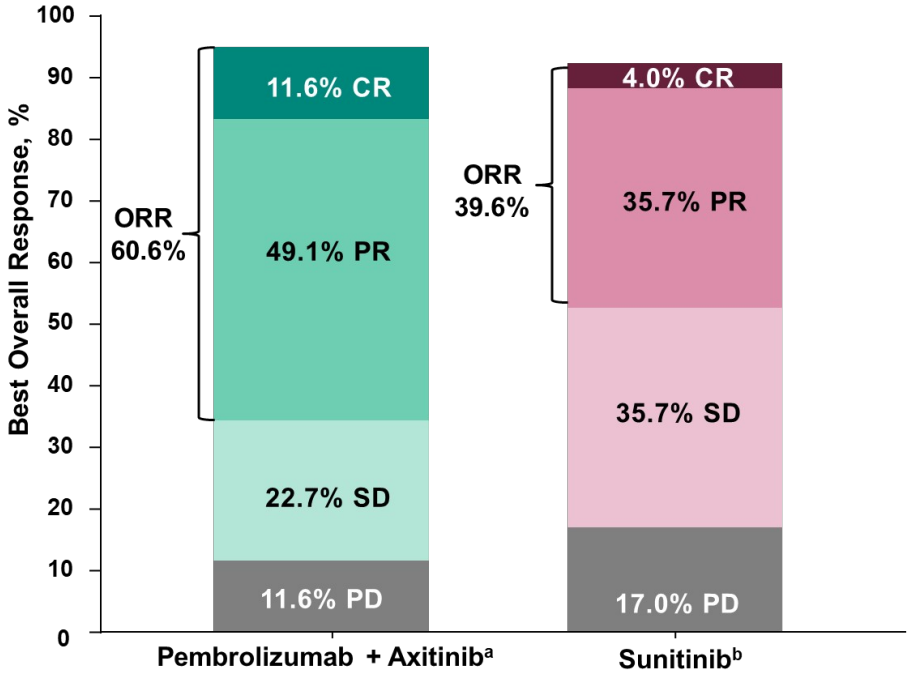
↓ *"M2-like" TAMs*

↑ *mature DCs*

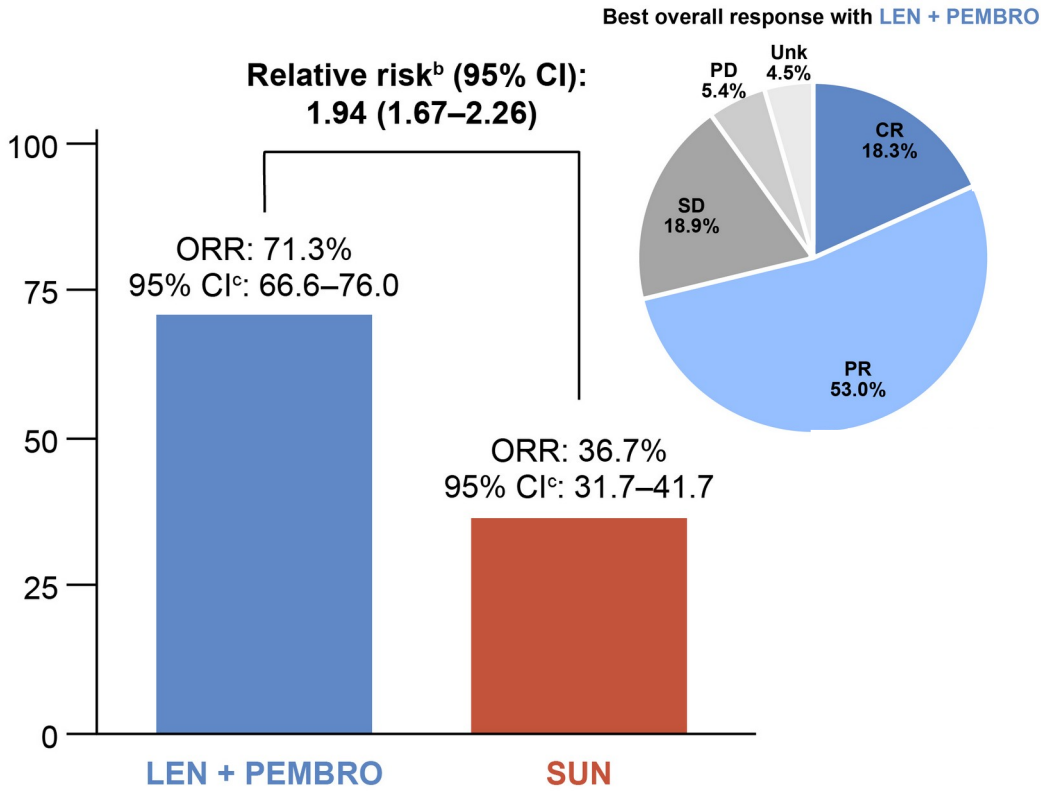
Fukumura, Nat Rev Clin Oncol, 2018

Is IO+TKI superior to TKI alone for front-line ccRCC treatment? Yes (↑ORR)

KN-426
(pembrolizumab+axitinib)



CLEAR
(pembrolizumab+lenvatinib)



Rini, ASCO 2023, LBA4501; Motzer & Hutson, ASCO 2023, 4501.

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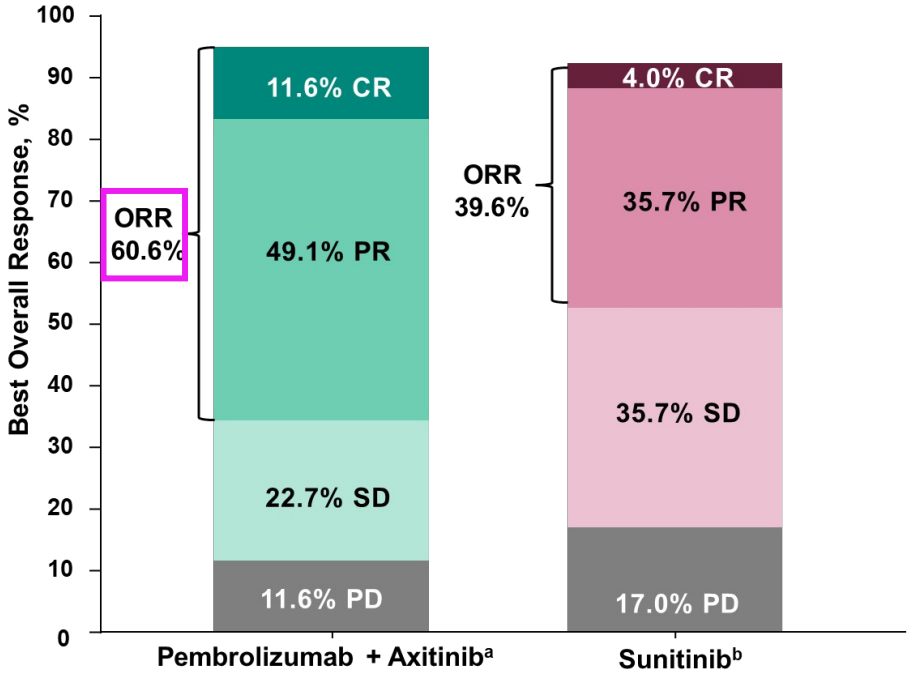

High ORR

CLEAR
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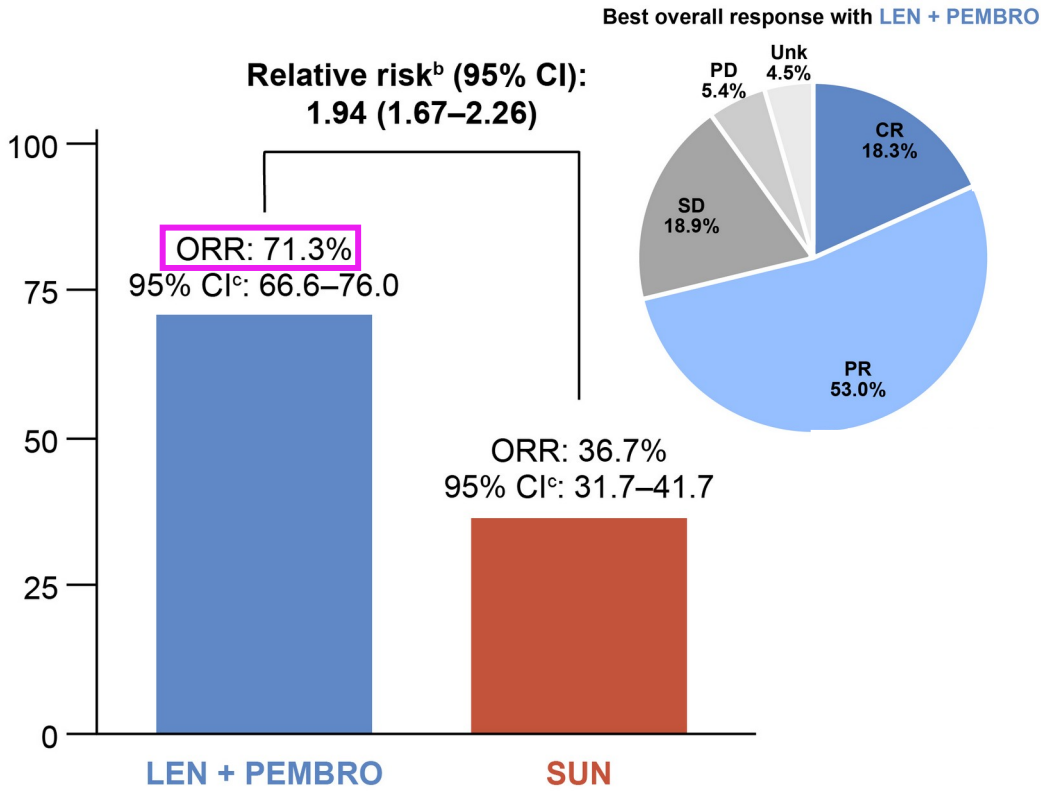

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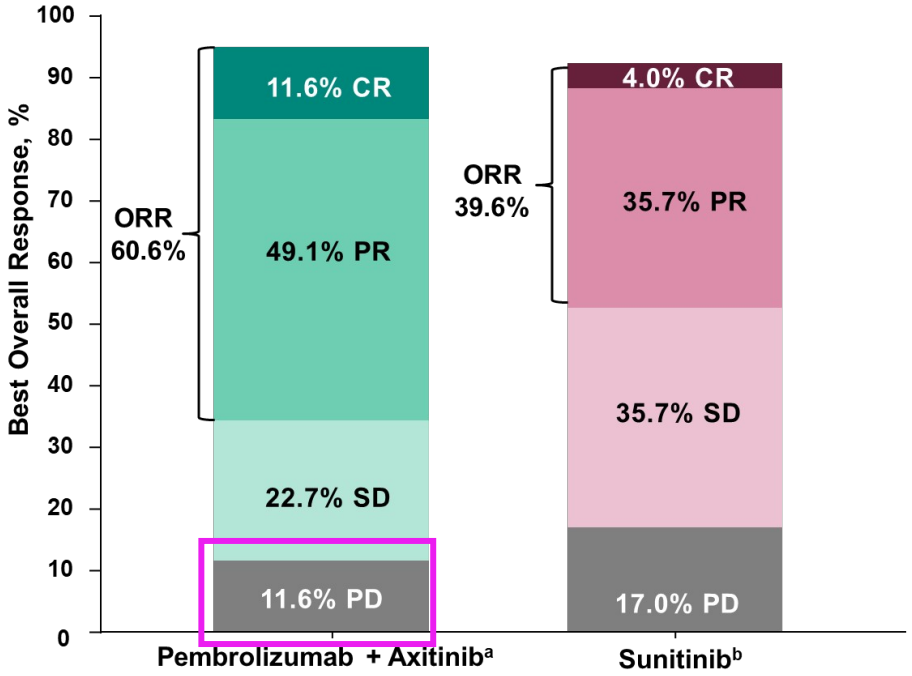
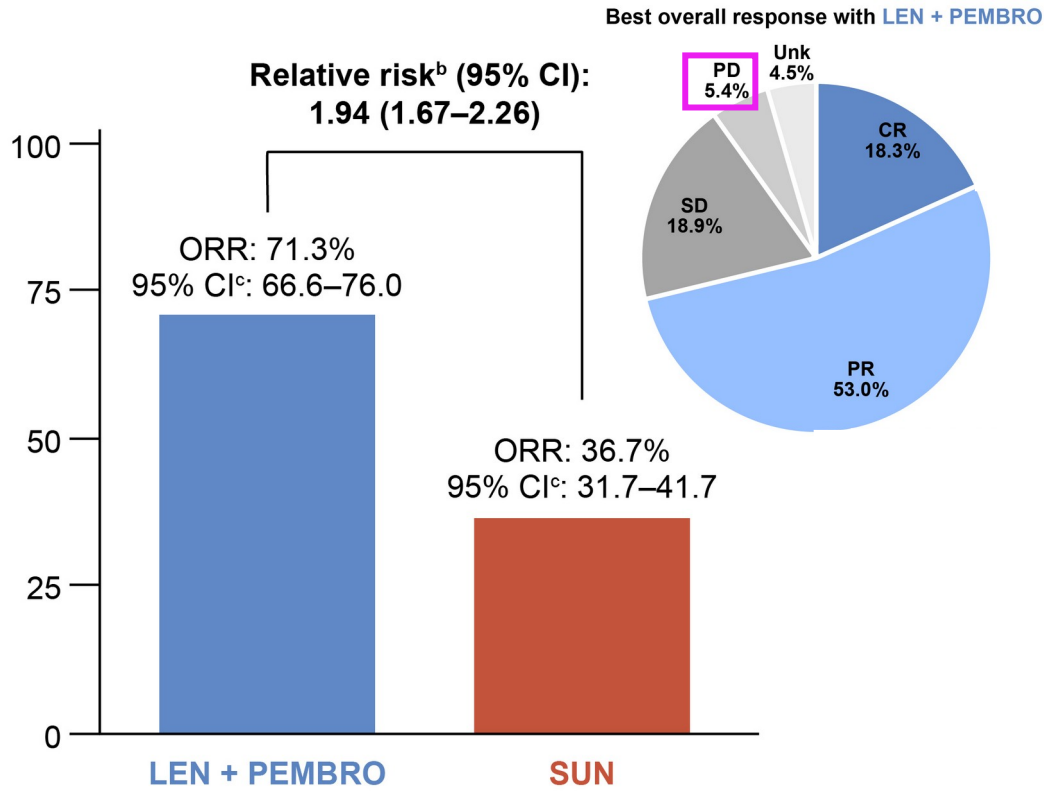


Low primary PD rate

CLEAR
(pembrolizumab+lenvatinib)



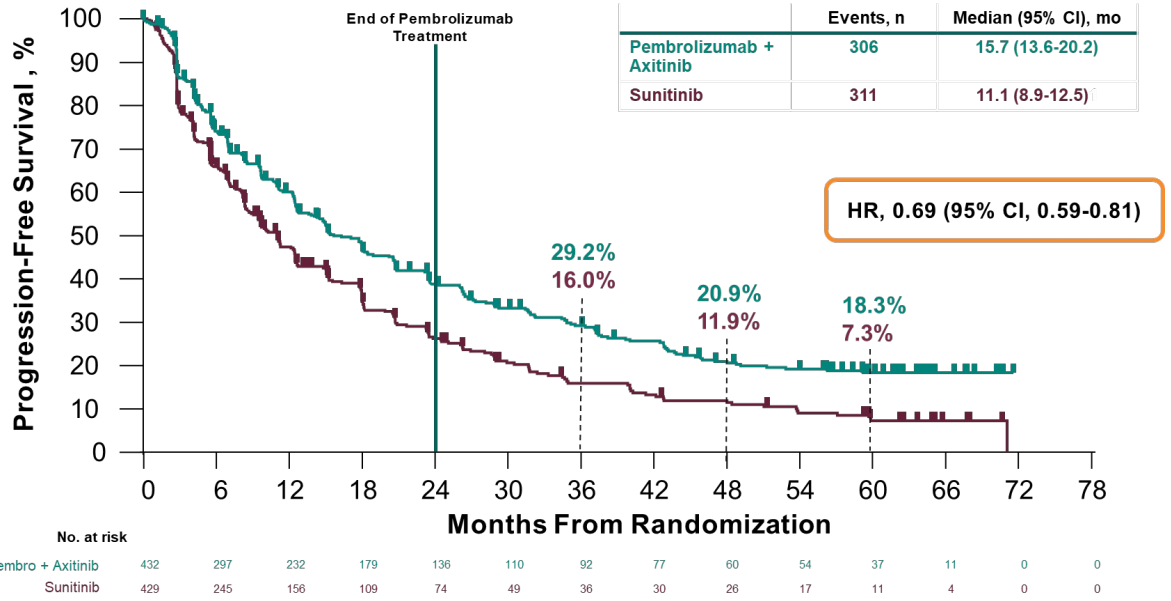
Rini, ASCO 2023, LBA4501; Motzer & Hutson, ASCO 2023, 4501.

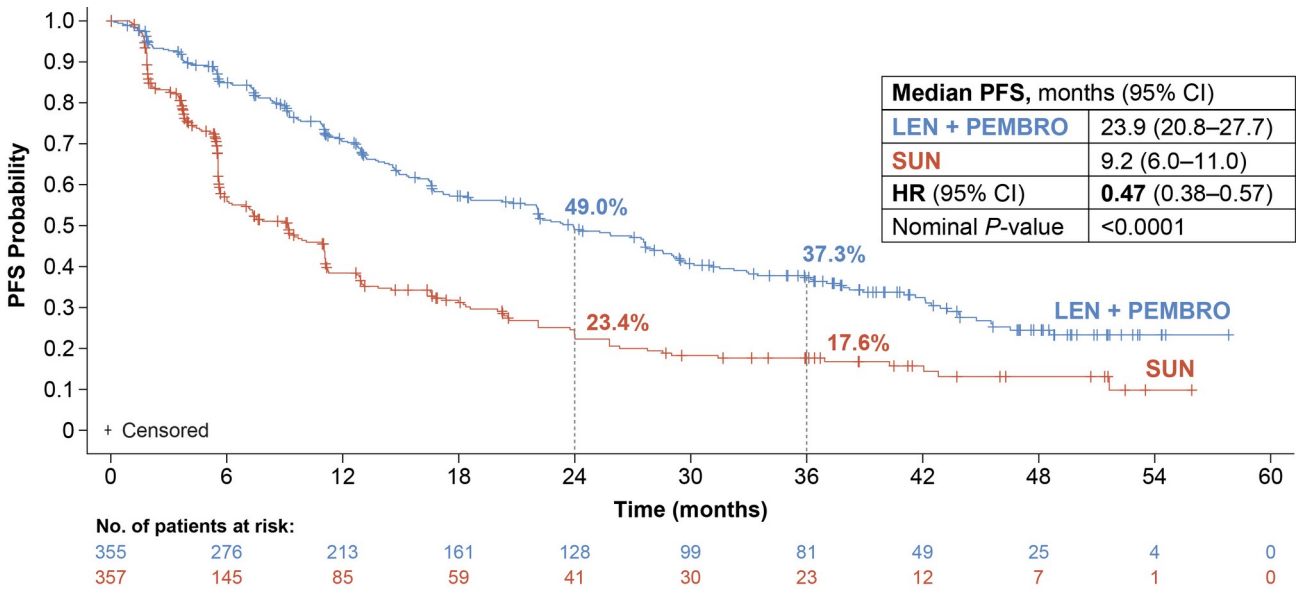
Is IO+TKI superior to TKI alone for front-line ccRCC treatment? Yes (↑PFS)

_KN-426_
(pembrolizumab+axitinib)

Strongly positive for PFS

CLEAR
(pembrolizumab+lenvatinib)





Rini, ASCO 2023, LBA4501; Motzer & Hutson, ASCO 2023, 4501.

Is IO+TKI superior to TKI alone for front-line ccRCC treatment? Yes (↑OS)

KN-426
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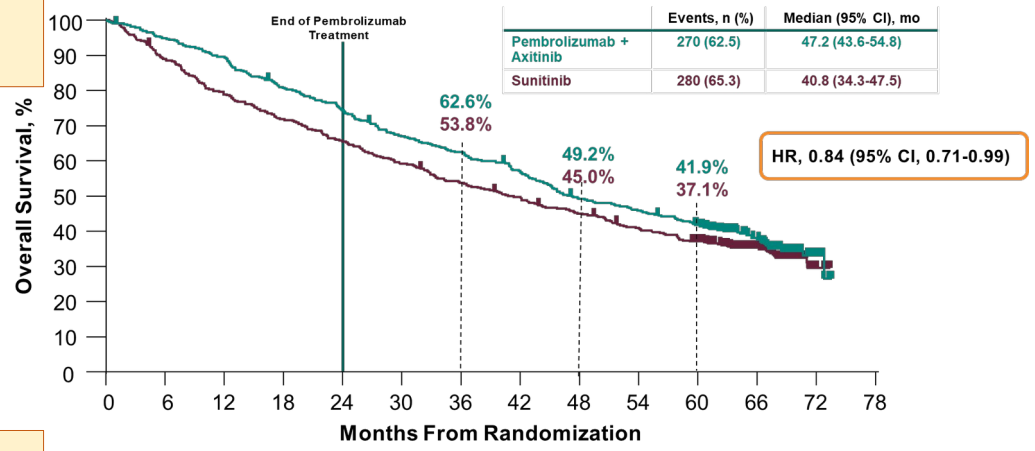

CLEAR
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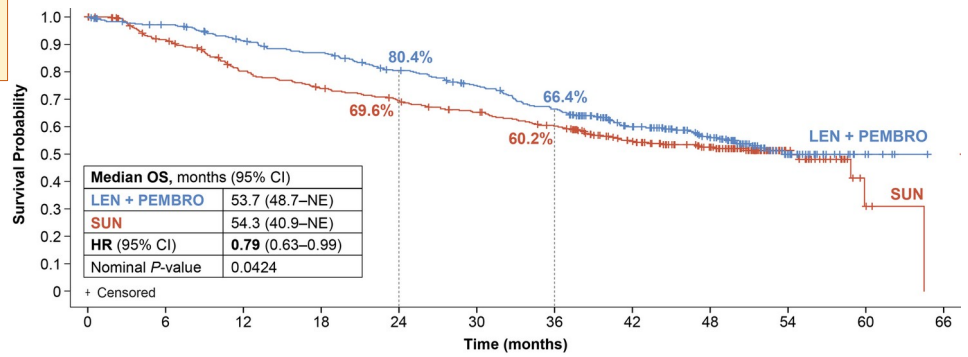

*Positive for OS, but questions around **durability****

Rini, ASCO 2023, LBA4501; Motzer & Hutson, ASCO 2023, 4501.

*Imbalance in subsequent therapies

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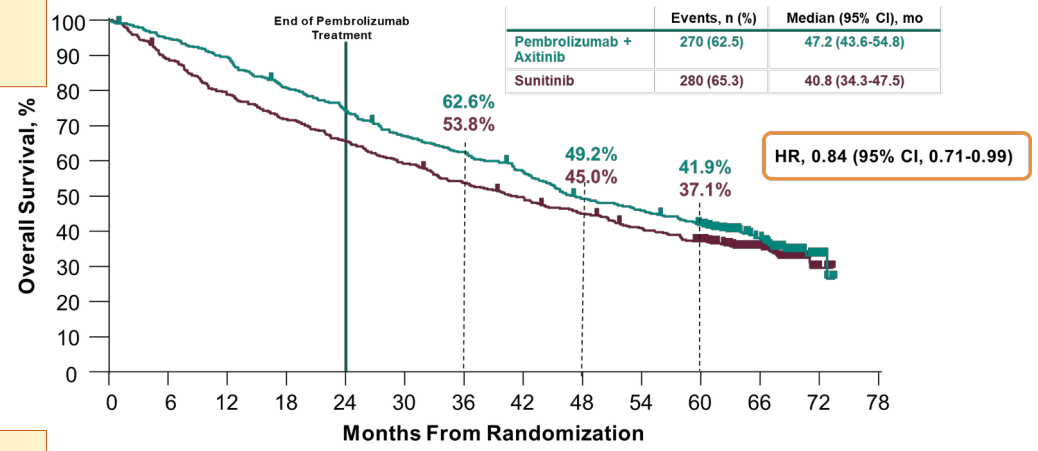

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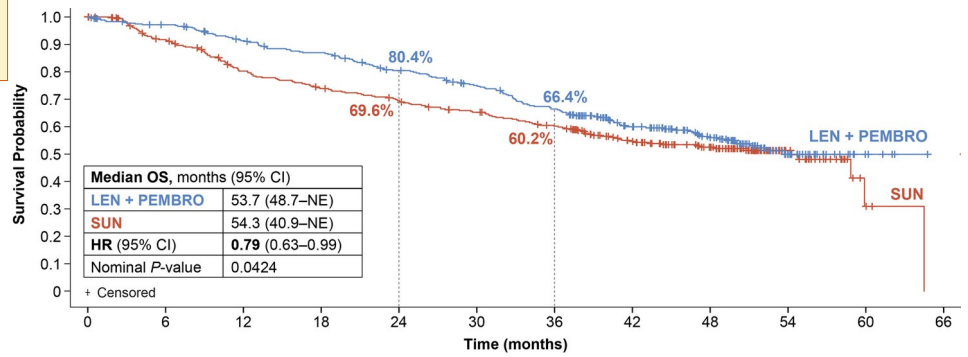
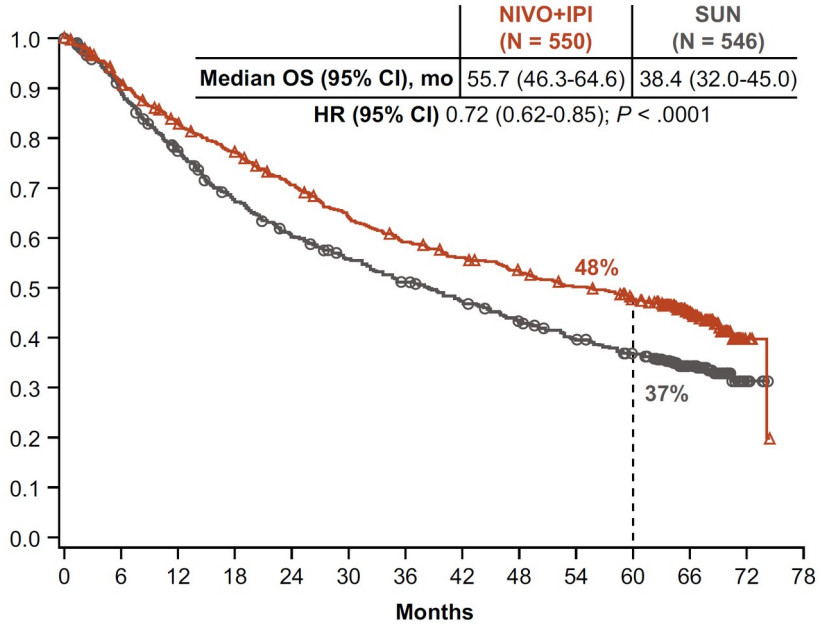


CM-214
(nivolumab+ipilimumab)

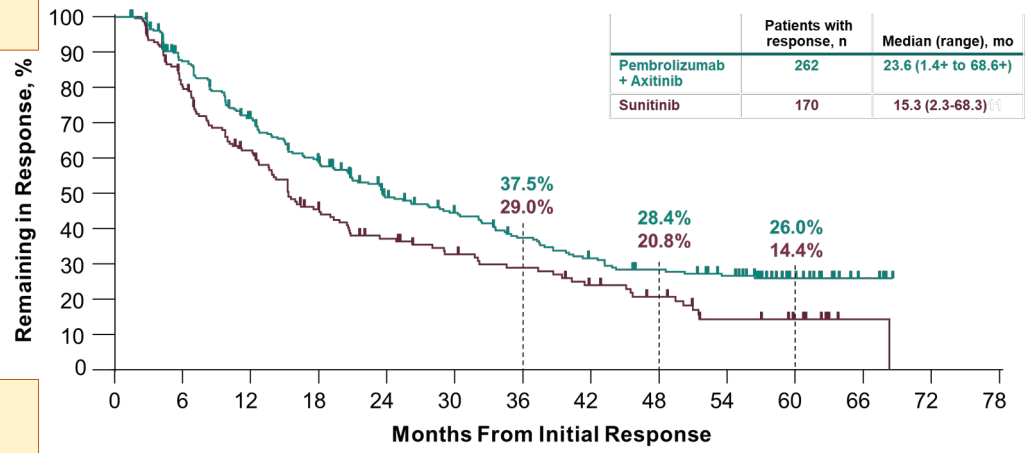


IO+IO maintains OS benefit over time

Rini, ASCO 2023, LBA4501; Motzer & Hutson, ASCO 2023, 4501, Motzer, Cancer, 2022.

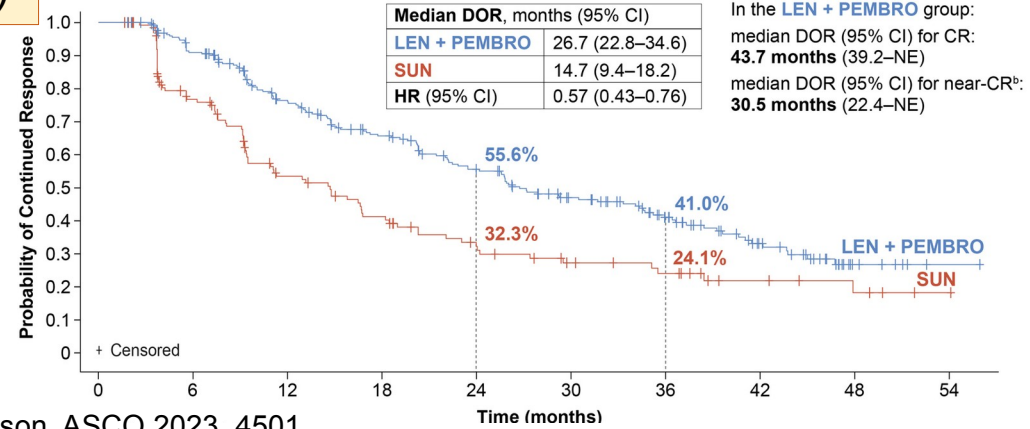
Are IO+TKI responses durable? Maybe

KN-426
(pembrolizumab+axitinib)



Median DOR: ~ 2 years

CLEAR
(pembrolizumab+lenvatinib)



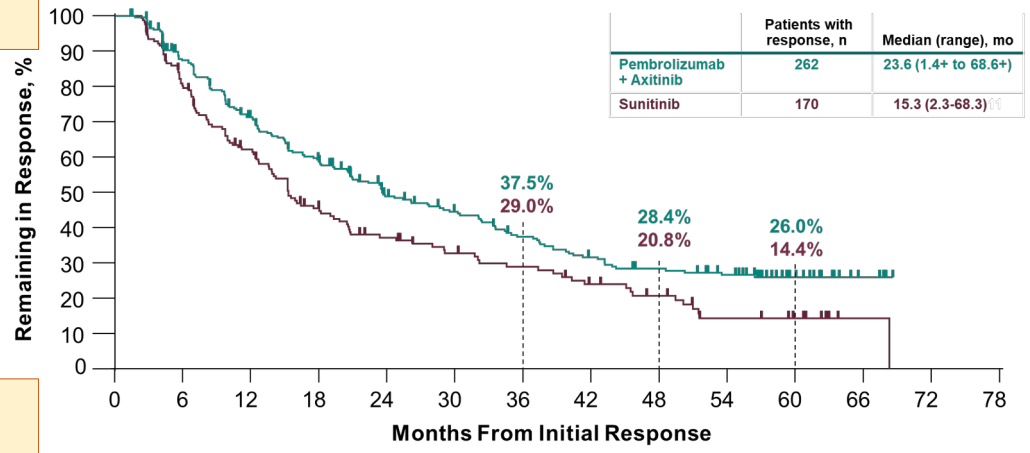
Lack of CTLA-4 blockade

Anti-PD-1 agent discontinued at 2 years

Rini, ASCO 2023, LBA4501; Motzer & Hutson, ASCO 2023, 4501.

Are IO+TKI responses durable? Maybe

KN-426
(pembrolizumab+axitinib)



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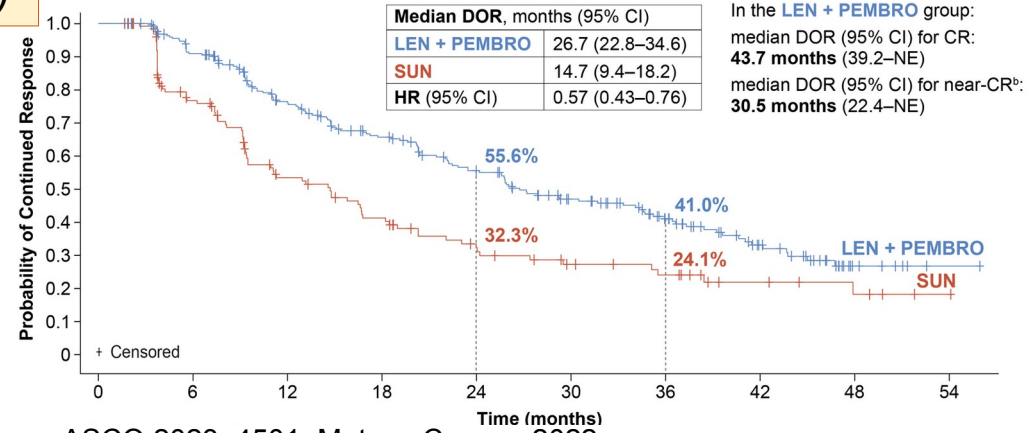
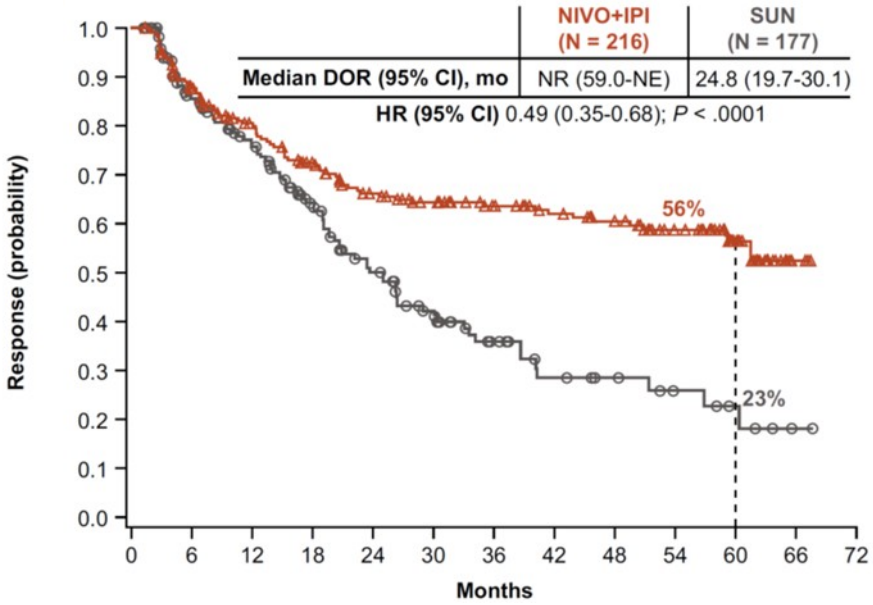


CM-214
(nivolumab+ipilimumab)

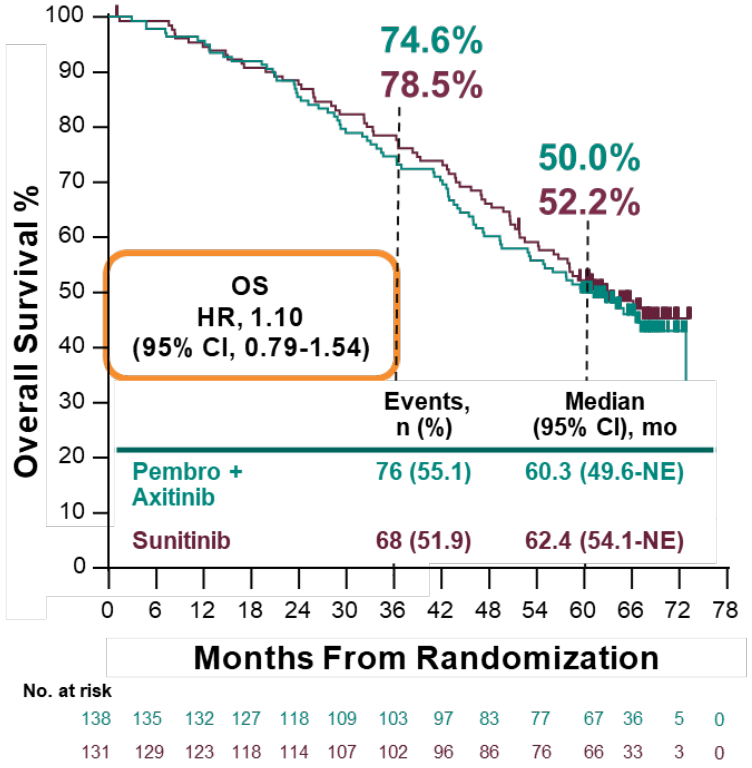


>50% of IO+IO response are durable

Rini, ASCO 2023, LBA4501; Motzer & Hutson, ASCO 2023, 4501, Motzer, Cancer, 2022.

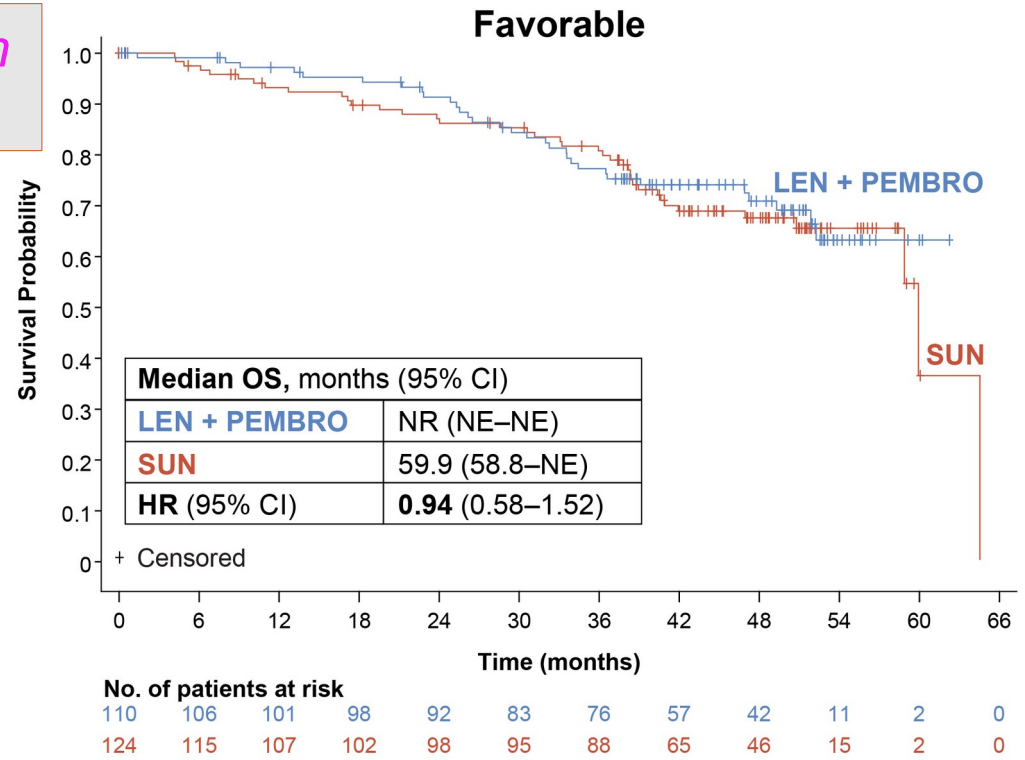
Does IO+TKI improve OS for patients with IMDC favorable risk RCC? Probably not

_KN-426_
(pembrolizumab+axitinib)



No OS benefit in IMDC favorable

CLEAR
(pembrolizumab+lenvatinib)



Rini, ASCO 2023, LBA4501; Motzer & Hutson, ASCO 2023, 4501.

Conclusions/Take-Away I

- **Do updated results from CLEAR and KN-426 change practice?**
  No, but they re-affirm it (for IMDC intermediate/poor risk)

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  No clear answer = need for additional investigation
  (IO+TKI, TKI alone, and pure IO should all be options here)

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- **Do updated results from CLEAR and KN-426 change practice?**
  No, but they re-affirm it (for IMDC intermediate/poor risk)

- **How do we treat patients with IMDC favorable risk disease?**
  No clear answer = need for additional investigation
  (IO+TKI, TKI alone, and pure IO should all be options here)

- **Does IO+TKI lead to durable responses or cures?**
  Not for most patients
  (no improvement in TFS; Chang…Regan, ASCO, 2023)

My front-line ccRCC treatment paradigm*

Oligometastatic?

****DISCLAIMER: views are my own**. Assumes clear cell RCC, patient who requires treatment (not active surveillance), no contraindication to IO, and IMDC intermediate/poor risk disease. Actual treatment decisions made collaboratively with the patient.*

PRESENTED BY: David A. Braun, MD, PhD @BraunMDPhD

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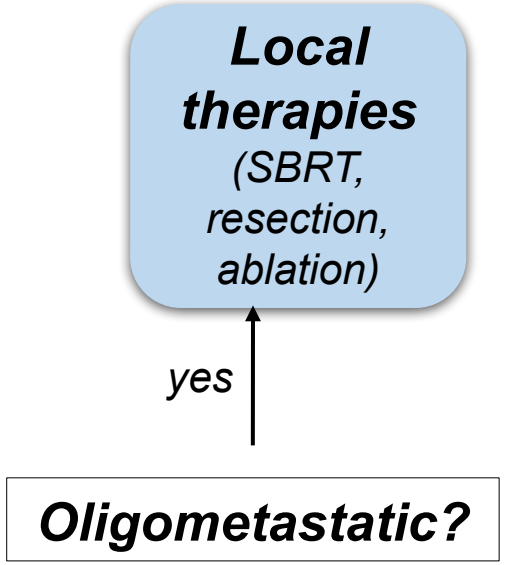

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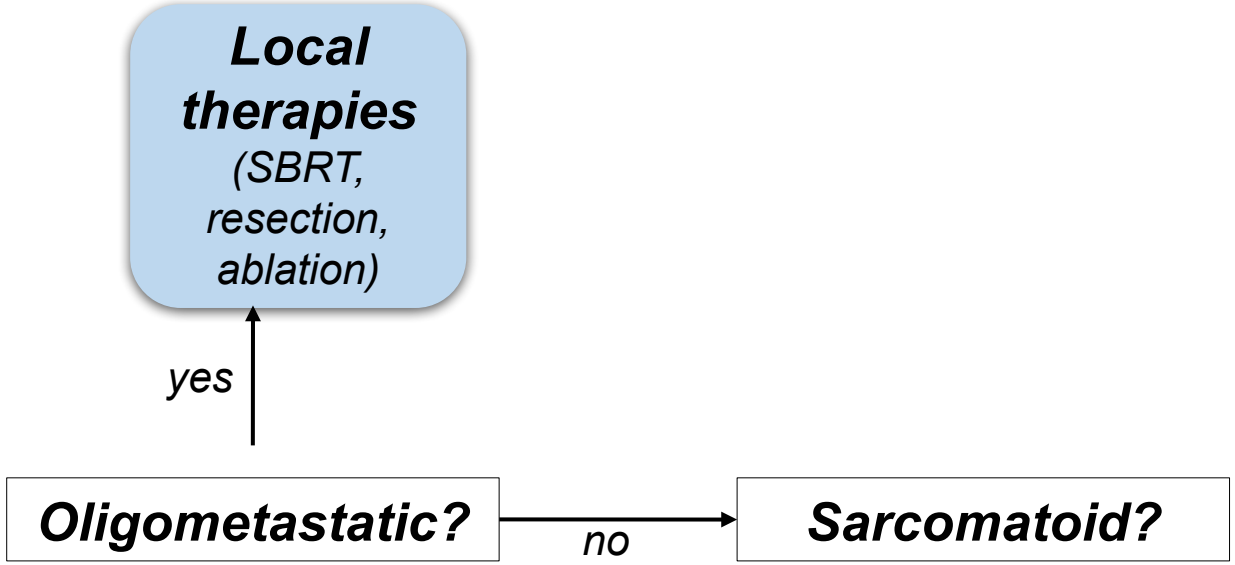

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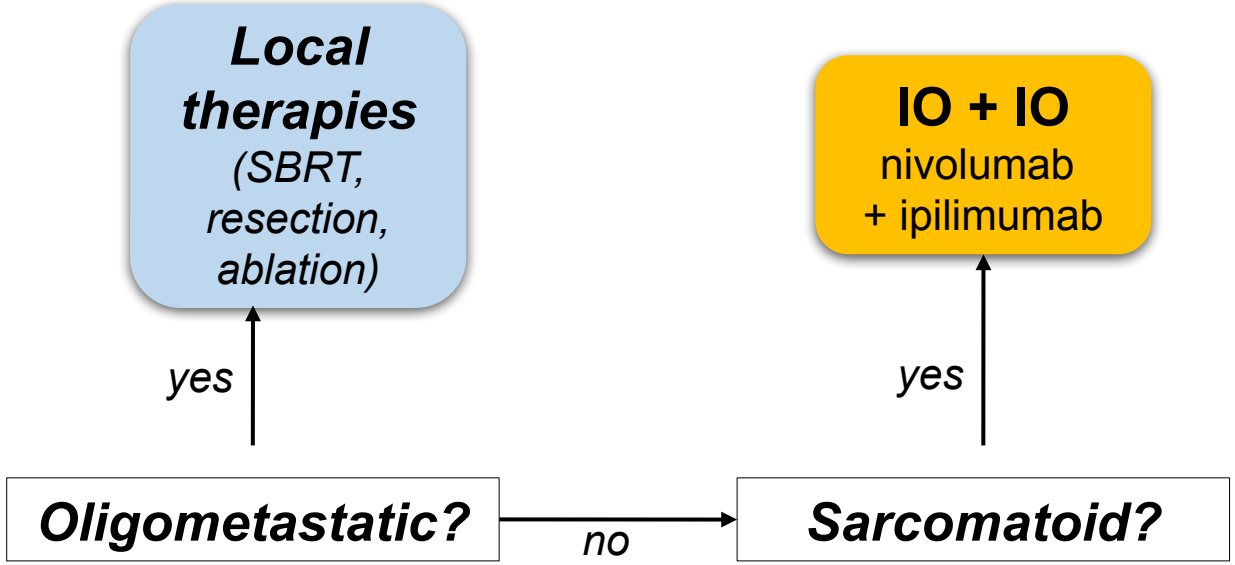

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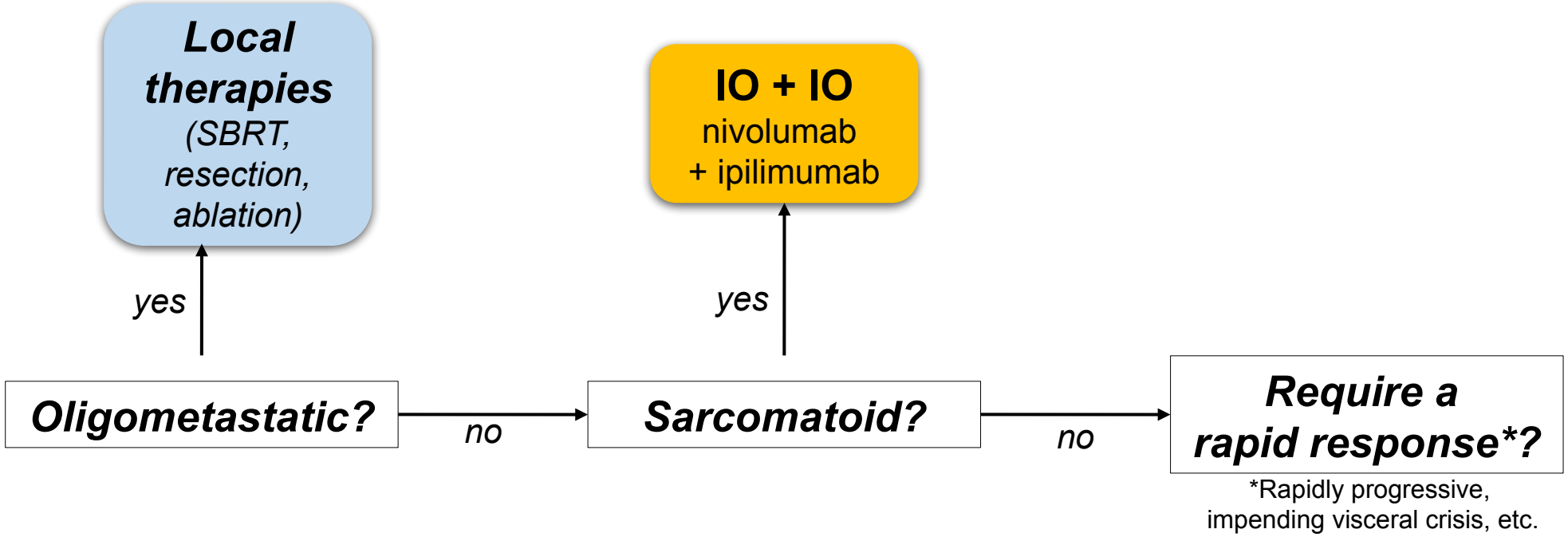

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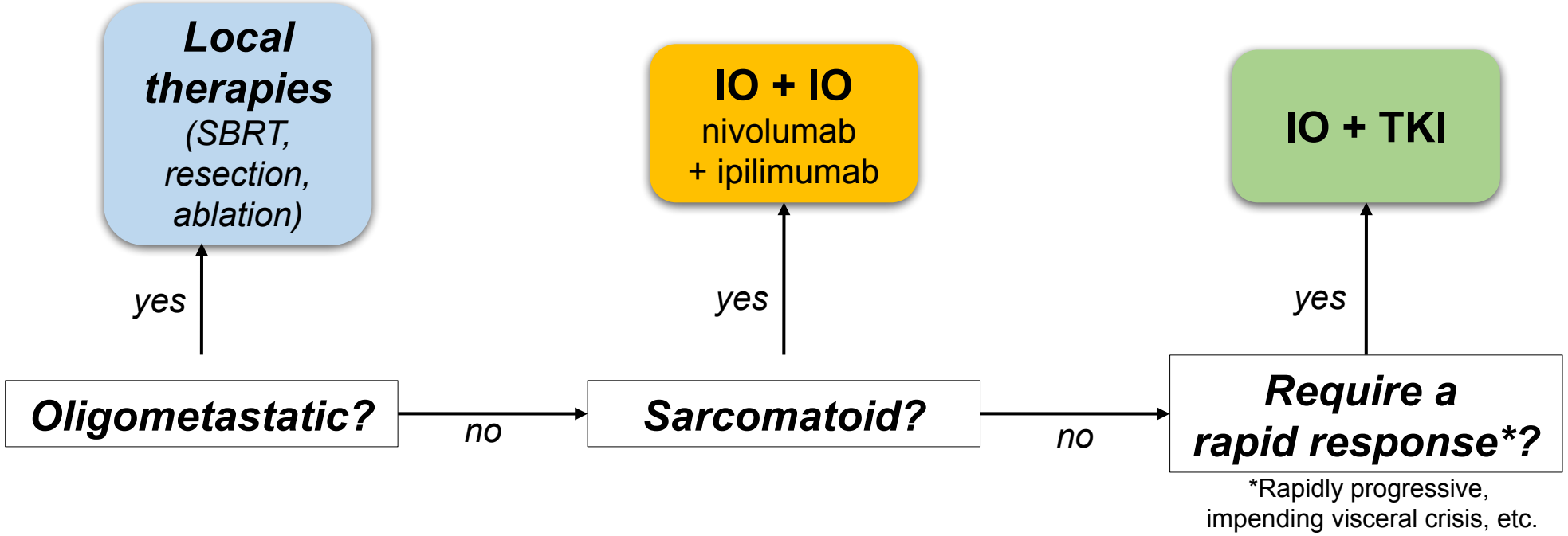

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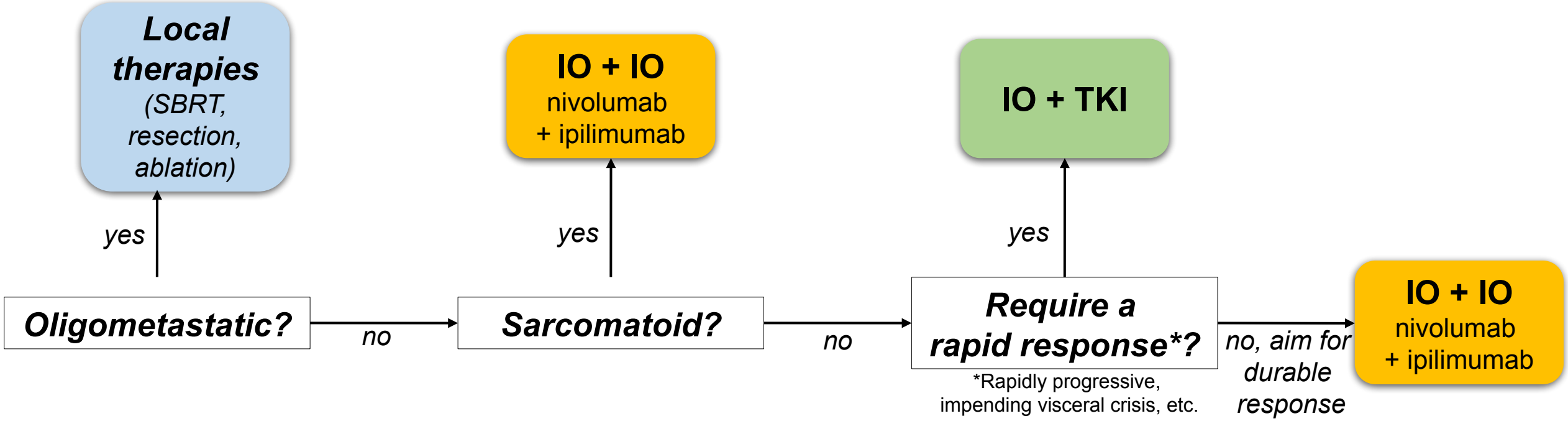

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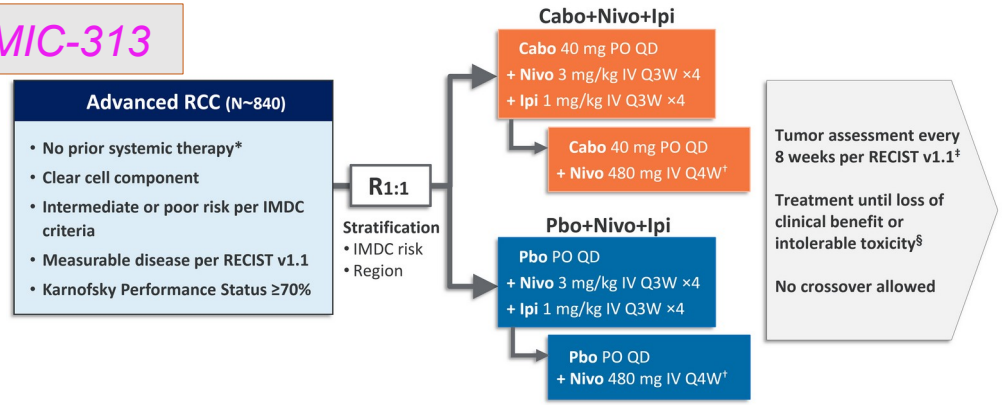
Next steps for front-line ccRCC?

Triplet therapy?

COSMIC-313



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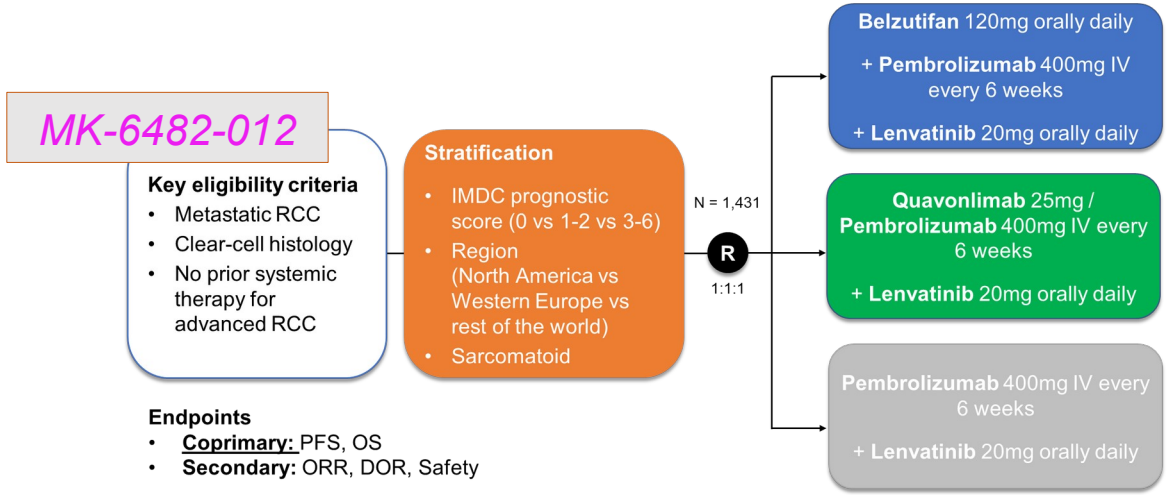

Choueiri, ESMO Congress, 2022;

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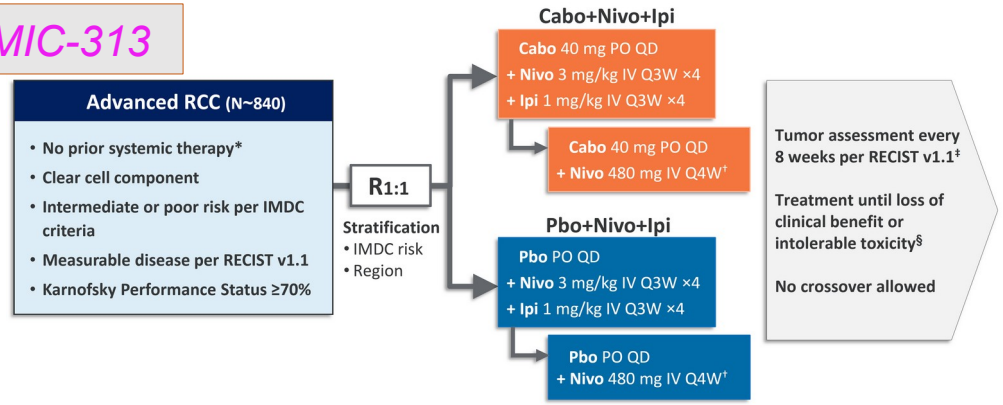
COSMIC-313



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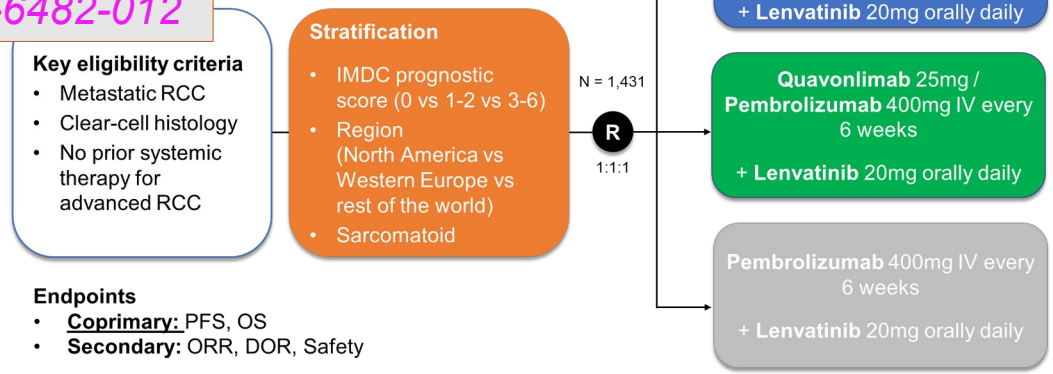
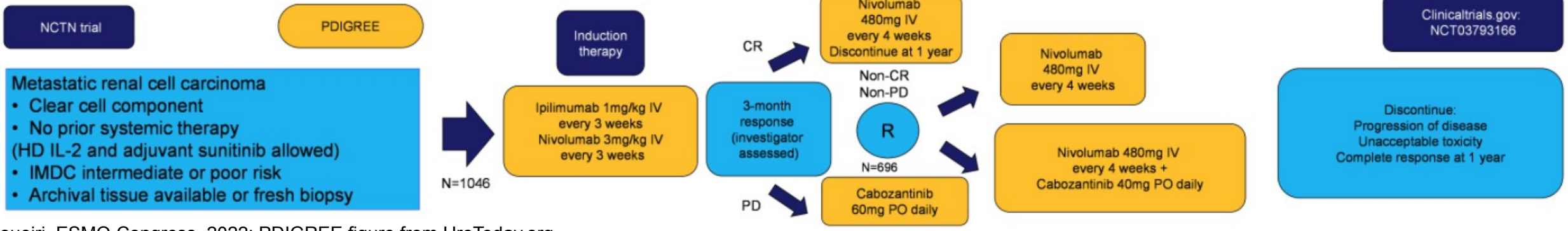


Adaptive trial designs

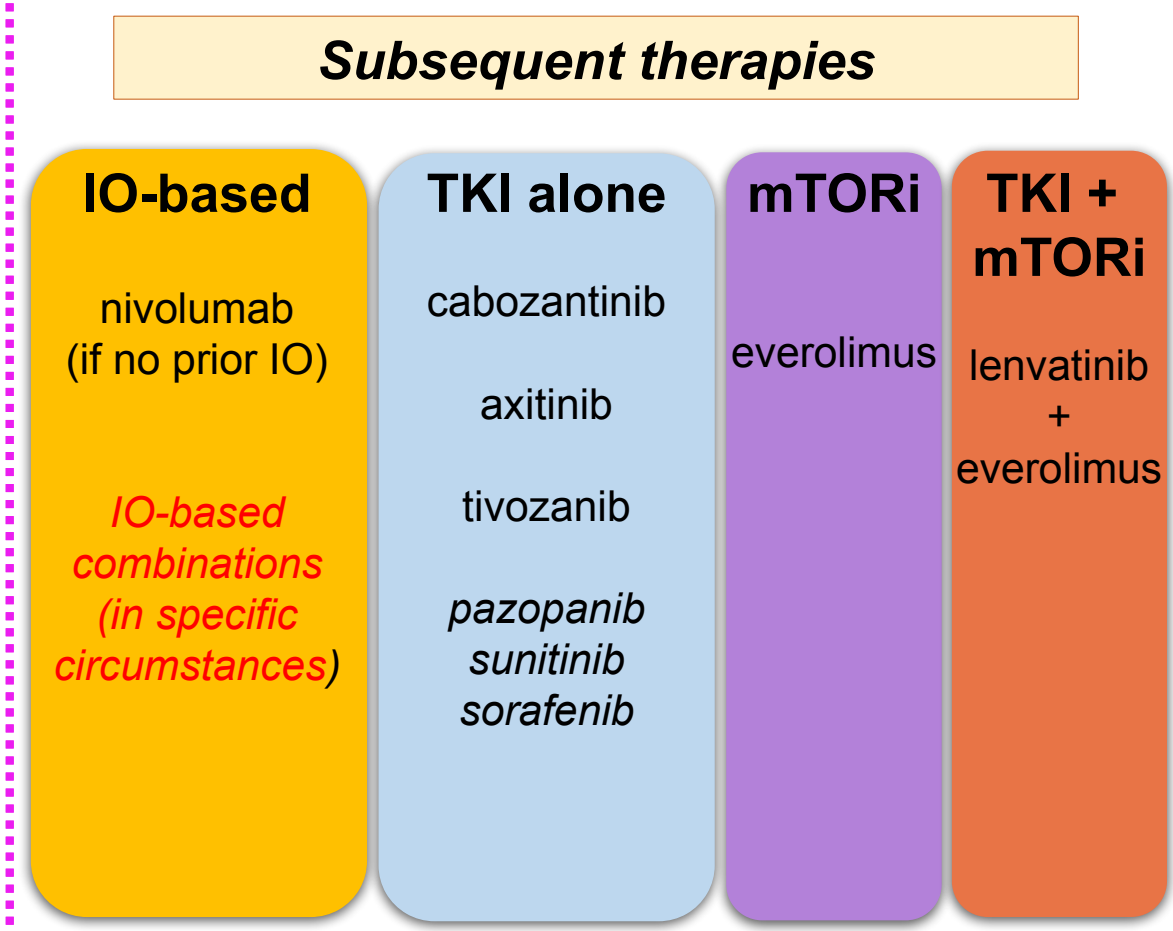
PDIGREE



Choueiri, ESMO Congress, 2022; PDIGREE figure from UroToday.org

Discussion for oral abstract session: genitourinary cancer – kidney and bladder

Abstract LBA4500 (Choueiri):
Efficacy and safety of atezolizumab plus cabozantinib vs cabozantinib alone after progression with prior immune checkpoint inhibitor (ICI) treatment in metastatic renal cell carcinoma (RCC): Primary PFS analysis from the phase 3, randomized, open-label CONTACT-03 study.

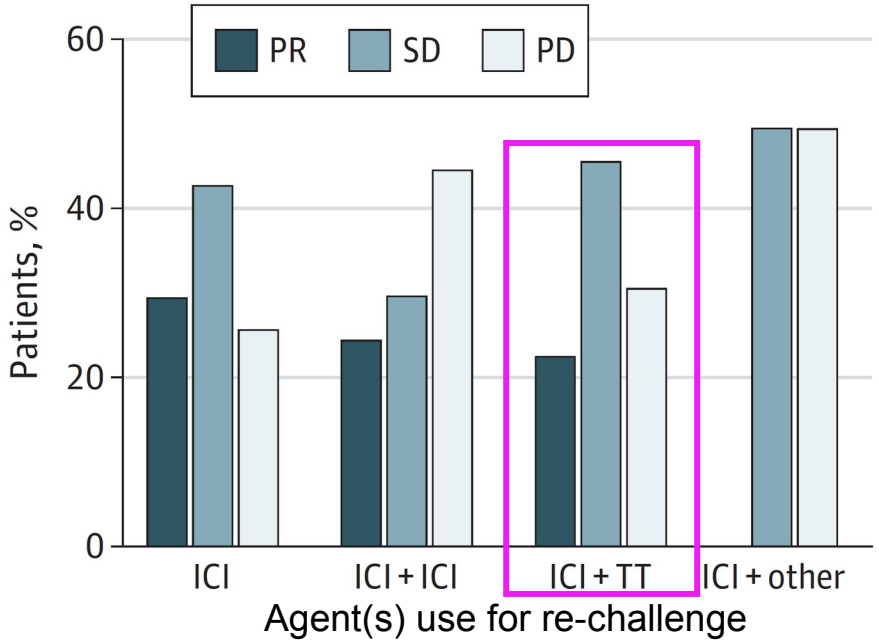


Abstract LBA4500 (Choueiri): CONTACT-03

Clinical Question:	Does “re-challenge” with ICI+TKI improve outcomes vs TKI alone in patients previously treated with ICI-based therapy?

Rechallenging with ICI post-ICI: clinical rationale

Retrospective



Propspective
(pembrolizumab+lenvatinib)

	Treatment naive* (n=22)	Previously treated ICI naive (n=17)	ICI pretreated* (n=104)
Objective response at week 24	16 (72·7%, 49·8–89·3)	7 (41·2%, 18·4–67·1)	58 (55·8%, 45·7–65·5)
Best overall response			
Complete response	0	0	0
Partial response	17 (77·3%)	9 (52·9%)	65 (62·5%)
Stable disease	5 (22·7%)	7 (41·2%)	31 (29·8%)
Progressive disease	0	1 (5·9%)	4 (3·8%)
Not evaluable	0	0	4 (3·8%)
Objective response	17 (77·3%, 54·6–92·2)	9 (52·9%, 27·8–77·0)	65 (62·5%, 52·5–71·8)
Duration of response, months	24·2 (10·3–37·7)	9·0 (3·5–NR)	12·5 (9·1–17·5)
Disease control	22 (100%, 84·6–100·0)	16 (94·1%, 71·3–99·9)	96 (92·3%, 85·4–96·6)
Clinical benefit	20 (90·9%, 70·8–98·9)	13 (76·5%, 50·1–93·2)	81 (77·9%, 68·7–85·4)
Time to response, months	1·4 (1·3–2·6)	2·8 (1·2–7·4)	2·7 (1·5–3·1)

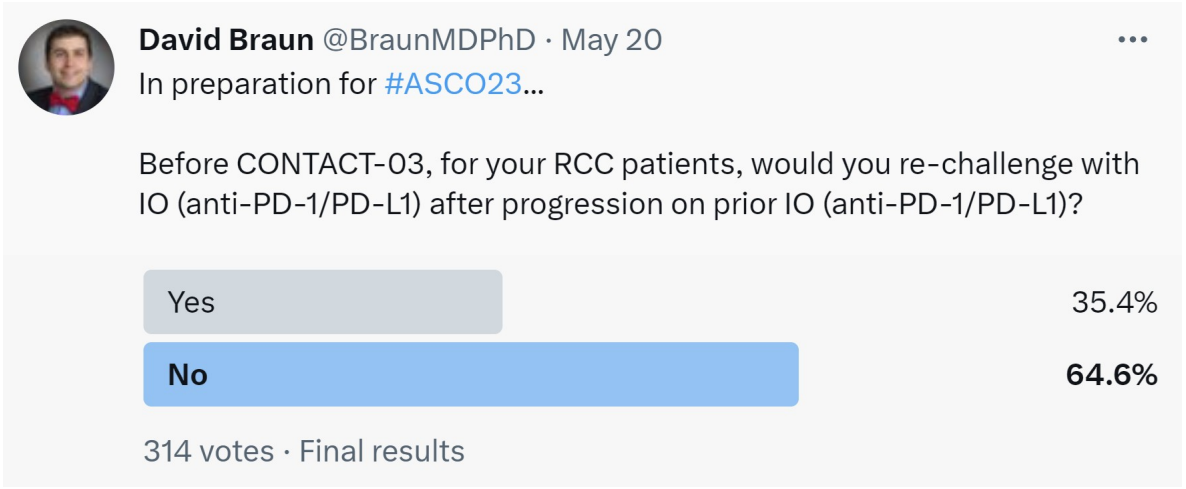
Ravi, JAMA Oncol, 2020; Lee, Lancet Oncol, 2021.

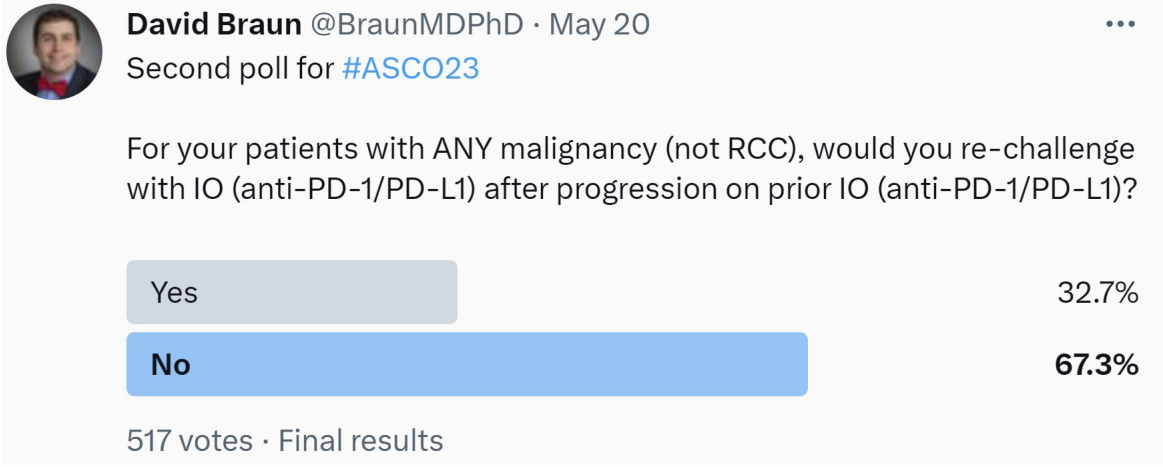
What is the current practice? results of a highly scientific poll***

***DISCLAIMER: this is a Twitter poll, and it is not at all scientific.

What is the current practice? results of a highly scientific poll***

An informal twitter poll: ~1/3 would re-challenge with IO after IO





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CONTACT-03: atezolizumab + cabozantinib vs cabozantinib alone in ICI-refractory RCC

- **Eligibility**
  - Advanced clear cell or non-clear cell
  - Progression on or after ICI (adjuvant, 1st or 2nd line)
- **Number of patients**
  - 522 randomized
- **Treatment**
  - Cabozantinib 60mg daily vs
    Cabozantinib **60**mg daily + atezolizumab 1200mg q3w
- **Key endpoints:**
  - Primary: PFS (central), OS
  - Secondary: PFS (investigator), ORR, DOR, safety

Choueiri, ASCO 2023, LBA4500.

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Mostly clear cell

Characteristic	Atezo +Cabo N = 263	Cabo N = 259
Histology		
Clear cell (no sarcomatoid)	78.7%	77.2%
Non-clear cell (no sarc)	11.4%	12.0%
Any sarcomatoid	9.5%	10.8%

Choueiri, ASCO 2023, LBA4500.

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Most recent ICI		
Adjuvant	0.4%	0.4%
1st line	54.8%	51.0%
2nd line	44.9%	47.9%

Very few post-adjuvant patients

Choueiri, ASCO 2023, LBA4500.

CONTACT-03: prior therapies

IO+IO most frequent in first line

	Atezo + Cabo (n=263)	Cabo (n=259)
First-line treatment, n (%)[a,b]	**262 (99.6)**	**258 (99.6)**
Ipilimumab + nivolumab	80 (30.5)	70 (27.1)
Sunitinib	77 (29.4)	72 (27.9)
Pazopanib	36 (13.7)	43 (16.6)
Axitinib + pembrolizumab	36 (13.7)	28 (10.9)
Nivolumab	6 (2.3)	10 (3.9)
Avelumab + axitinib	7 (2.7)	6 (2.3)
Bempegaldesleukin + nivolumab	3 (1.1)	9 (3.5)
Lenvatinib + pembrolizumab	6 (2.3)	3 (1.2)
Sorafenib	3 (1.1)	1 (0.4)
Second-line treatment, n (%)[a,b]	**119 (45.2)**	**125 (48.3)**
Nivolumab	104 (87.4)	116 (92.8)
Ipilimumab + nivolumab	4 (3.4)	3 (2.4)
Axitinib + pembrolizumab	2 (1.7)	3 (2.4)
Adjuvant treatment, n (%)[a,b]	**8 (3.0)**	**4 (1.5)**
Sunitinib	2 (25)	2 (50)

Choueiri, ASCO 2023, LBA4500.

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ICI monotherapy most common in second line

Choueiri, ASCO 2023, LBA4500.

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~20% with prior IO+TKI

Choueiri, ASCO 2023, LBA4500.

Does re-challenge with ICI improve response? No

No difference in:
- *Response*
- *Primary PD rate*
- *Disease control*
- *Duration of response*

	RECIST 1.1 per central review[a]		RECIST 1.1 per investigator[a]	
	Atezo + Cabo (n=259)	Cabo (n=254)	Atezo + Cabo (n=263)	Cabo (n=259)
Confirmed objective response, n, (%) [95% CI]	105 (40.5) [34.5, 46.8]	104 (40.9) [34.8, 47.3]	100 (38.0) [32.1, 44.2]	108 (41.7) [35.6, 48.0]
Complete response, n (%)	0	2 (0.8)	4 (1.5)	2 (0.8)
Partial response, n (%)	105 (40.5)	102 (40.2)	96 (36.5)	106 (40.9)
Stable disease, n (%)	131 (50.6)	121 (47.6)	127 (48.3)	120 (46.3)
Progressive disease, n (%)	11 (4.2)	13 (5.1)	24 (9.1)	17 (6.6)
Not evaluable or missing, n (%)	12 (4.6)	16 (6.3)	12 (4.6)	14 (5.4)
Ongoing response at data cutoff, n/N (%)[b]	53/105 (50.5)	55/104 (52.9)	58/100 (58.0)	48/108 (44.4)
Median duration of response (range), mo	12.7 (2.1+ to 22.9+)	14.8 (2.3+ to 25.6+)	NE (2.1+ to 23.2+)	12.2 (2.1+ to 25.6+)

Choueiri, ASCO 2023, LBA4500.

Is cabozantinib effective after prior ICI? Yes

METEOR: ORR 21%

CaboPoint: ORR 29.5%

	RECIST 1.1 per central review[a]		RECIST 1.1 per investigator[a]	
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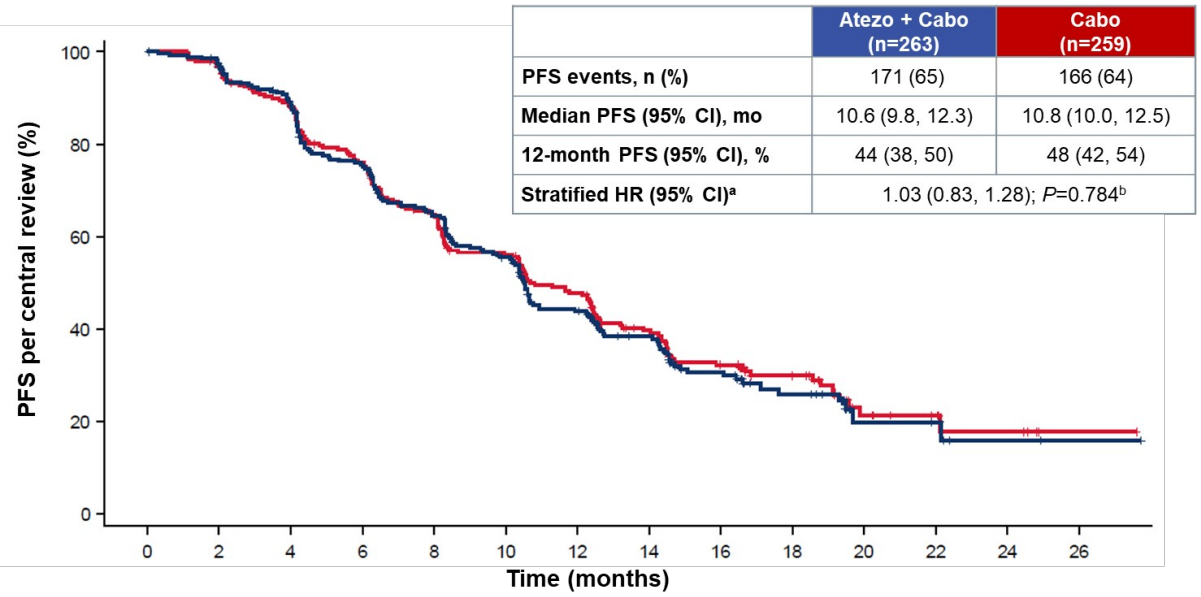
Choueiri, ASCO 2023, LBA4500; Choueiri, N Engl J Med, 2015; Albiges, ASCO GU 2023.

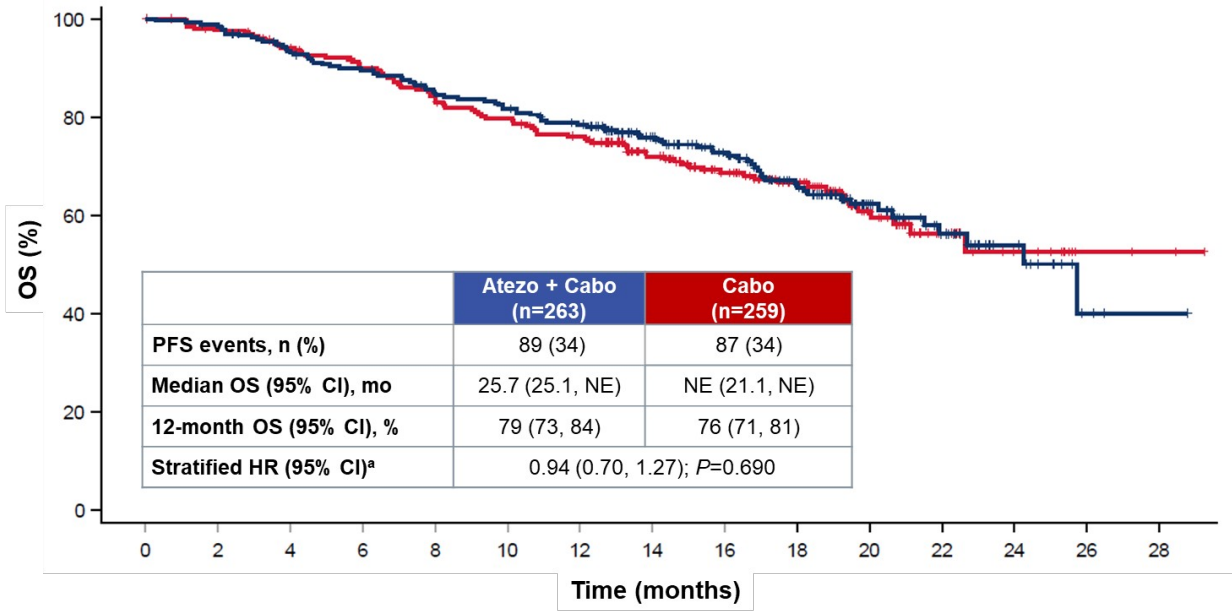
Does re-challenge with ICI improve survival? No

PFS



	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	171 (65)	166 (64)
Median PFS (95% CI), mo	10.6 (9.8, 12.3)	10.8 (10.0, 12.5)
12-month PFS (95% CI), %	44 (38, 50)	48 (42, 54)
Stratified HR (95% CI)[a]	1.03 (0.83, 1.28); *P*=0.784[b]	

OS

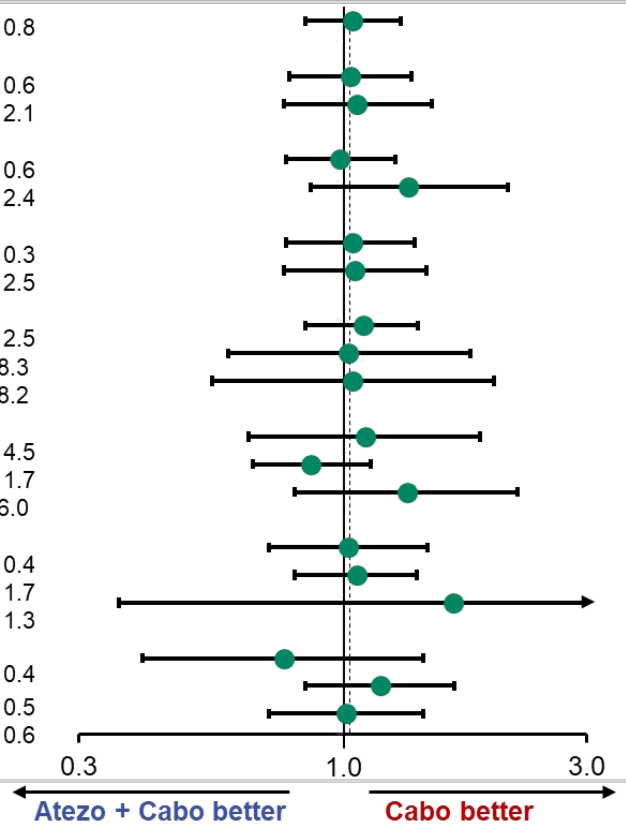


	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	89 (34)	87 (34)
Median OS (95% CI), mo	25.7 (25.1, NE)	NE (21.1, NE)
12-month OS (95% CI), %	79 (73, 84)	76 (71, 81)
Stratified HR (95% CI)[a]	0.94 (0.70, 1.27); *P*=0.690	

Choueiri, ASCO 2023, LBA4500.

Did any subgroup benefit? No

Characteristic[a]	Atezo + Cabo: No. of PFS events/patients	Atezo + Cabo: Median PFS, mo	Cabo: No. of PFS events/patients	Cabo: Median PFS, mo	PFS HR (95% CI)[b]
All patients	171/263	10.5	166/259	10.8	1.04 (0.84, 1.29)
Age					
<65 y	104/153	10.4	96/144	10.6	1.03 (0.78, 1.36)
≥65 y	67/110	10.6	115/225	12.1	1.06 (0.76, 1.49)
Sex					
Male	130/204	10.6	197/401	10.6	0.98 (0.77, 1.26)
Female	41/59	10.1	62/121	12.4	1.34 (0.86, 2.10)
Most recent ICI therapy					
First line	98/144	9.9	87/132	10.3	1.04 (0.77, 1.38)
Second line	72/118	12.4	77/124	12.5	1.05 (0.76, 1.45)
Histology					
Dominant clear cell	128/207	10.7	117/200	12.5	1.09 (0.84, 1.40)
Dominant non-clear cell	25/30	6.3	27/31	8.3	1.02 (0.59, 1.77)
Any sarcomatoid component	18/25	8.3	22/28	8.2	1.04 (0.55, 1.97)
IMDC score					
0	25/49	14.3	34/69	14.5	1.10 (0.65, 1.85)
1-2	109/172	10.8	104/153	11.7	0.86 (0.66, 1.13)
3-6	36/41	4.9	28/36	6.0	1.33 (0.80, 2.20)
Prior lines of VEGFR-TKI					
0	61/93	9.7	60/95	10.4	1.02 (0.71, 1.46)
1	107/166	10.6	102/159	11.7	1.06 (0.80, 1.39)
2	3/4	6.7	4/5	11.3	1.64 (0.36, 7.47)
Best response to most recent ICI					
CR/PR	25/47	11.9	16/30	10.4	0.76 (0.40, 1.43)
SD	70/104	10.5	65/97	10.5	1.18 (0.84, 1.65)
PD	63/92	10.4	63/95	10.6	1.01 (0.71, 1.43)



CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
[a] Categories with ≤2 patients are not shown. [b] Unstratified.

Choueiri, ASCO 2023, LBA4500.

Is re-challenge with ICI+TKI more toxic than TKI alone? Yes

Adverse event, n (%)	Atezo + Cabo (n=262)	Cabo (n=256)
Any-cause AE	262 (100)	254 (99.2)
Any-cause treatment-related AE	252 (96.2)	249 (97.3)
Grade 3 or 4 AE	177 (67.6)	158 (61.7)
Grade 3 or 4 treatment-related AE	145 (55.3)	121 (47.3)
Death due to AE	17 (6.5)	9 (3.5)
Death due to treatment-related AE	3 (1.1)[a]	0
Serious AE	126 (48.1)	84 (32.8)
Serious treatment-related AE	63 (24.0)	30 (11.7)
AE leading to withdrawal from a trial drug	41 (15.6)	10 (3.9)
AE leading to withdrawal from atezo	29 (11.1)	–
AE leading to withdrawal from cabo	25 (9.5)	10 (3.9)
AE leading to interruption or reduction of a trial drug	240 (91.6)	223 (87.1)
AE leading to interruption of atezo[b]	159 (60.7)	–
AE leading to interruption or reduction of cabo	234 (89.3)	223 (87.1)

Choueiri, ASCO 2023, LBA4500.

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Higher G3-4 AE

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Is re-challenge with ICI+TKI more toxic than TKI alone? Yes

Three treatment-related deaths

Two immune-related deaths

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Choueiri, ASCO 2023, LBA4500.

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Double the rate of serious AEs

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Double the rate of withdrawal from cabo

Limitations of CONTACT-03

- **Anti-PD-L1 instead of anti-PD-1**
  Anti-PD-L1 may be less active in RCC

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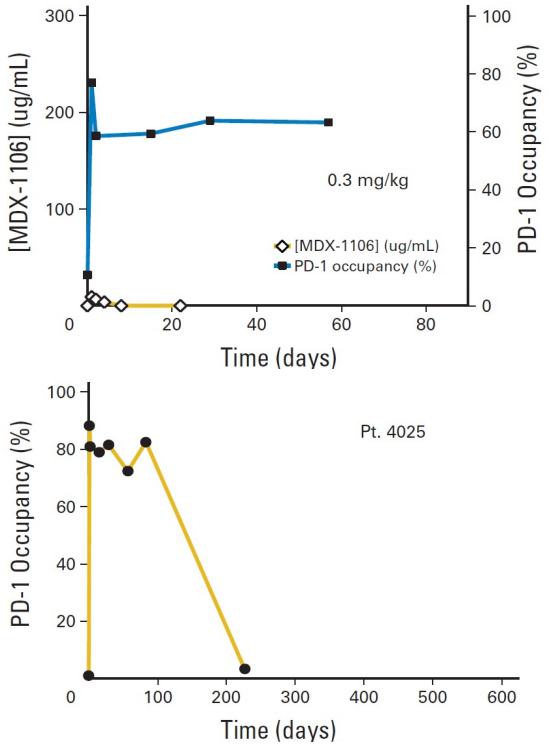
- **Anti-PD-L1 instead of anti-PD-1**
  Anti-PD-L1 may be less active in RCC

- **IO re-challenge is *immediately* after prior IO**
  Long-term PD-1 receptor occupancy
  Does not answer delayed re-challenge

Long-term PD-1 receptor occupancy
Brahmer, J Clin Oncol, 2010



Limitations of CONTACT-03

- **Anti-PD-L1 instead of anti-PD-1**
  Anti-PD-L1 may be less active in RCC

- **IO re-challenge is *immediately* after prior IO**
  Long-term PD-1 receptor occupancy
  Does not answer delayed re-challenge

- **Very few patients treated after adjuvant pembrolizumab**
  Does not answer question of optimal treatment after adjuvant IO
  (need trials for this)

Abstract LBA4500 (Choueiri): CONTACT-03

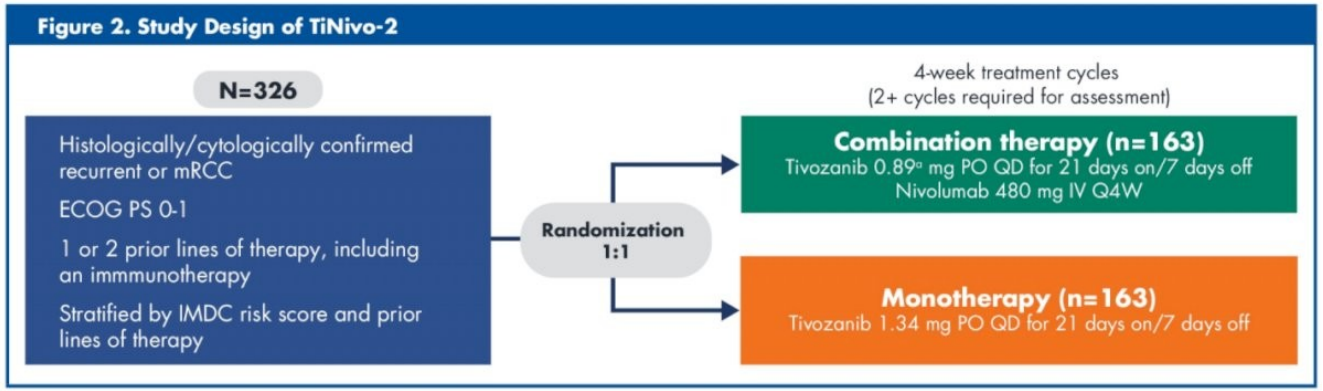
Clinical Question:	Does “re-challenge” with ICI+TKI improve outcomes vs TKI alone in patients previously treated with ICI-based therapy?
Findings:	• Addition of atezolizumab to cabozantinib did NOT improve response or progression-free survival vs cabozantinib alone • Atezolizumab + cabozantinib had significantly higher G3-4 AEs • Cabozantinib is effective therapy for ICI-refractory RCC (ORR ~40%)

Could IO post-IO still be effective in RCC?

Maybe

Use anti-PD-1 (not anti-PD-L1)

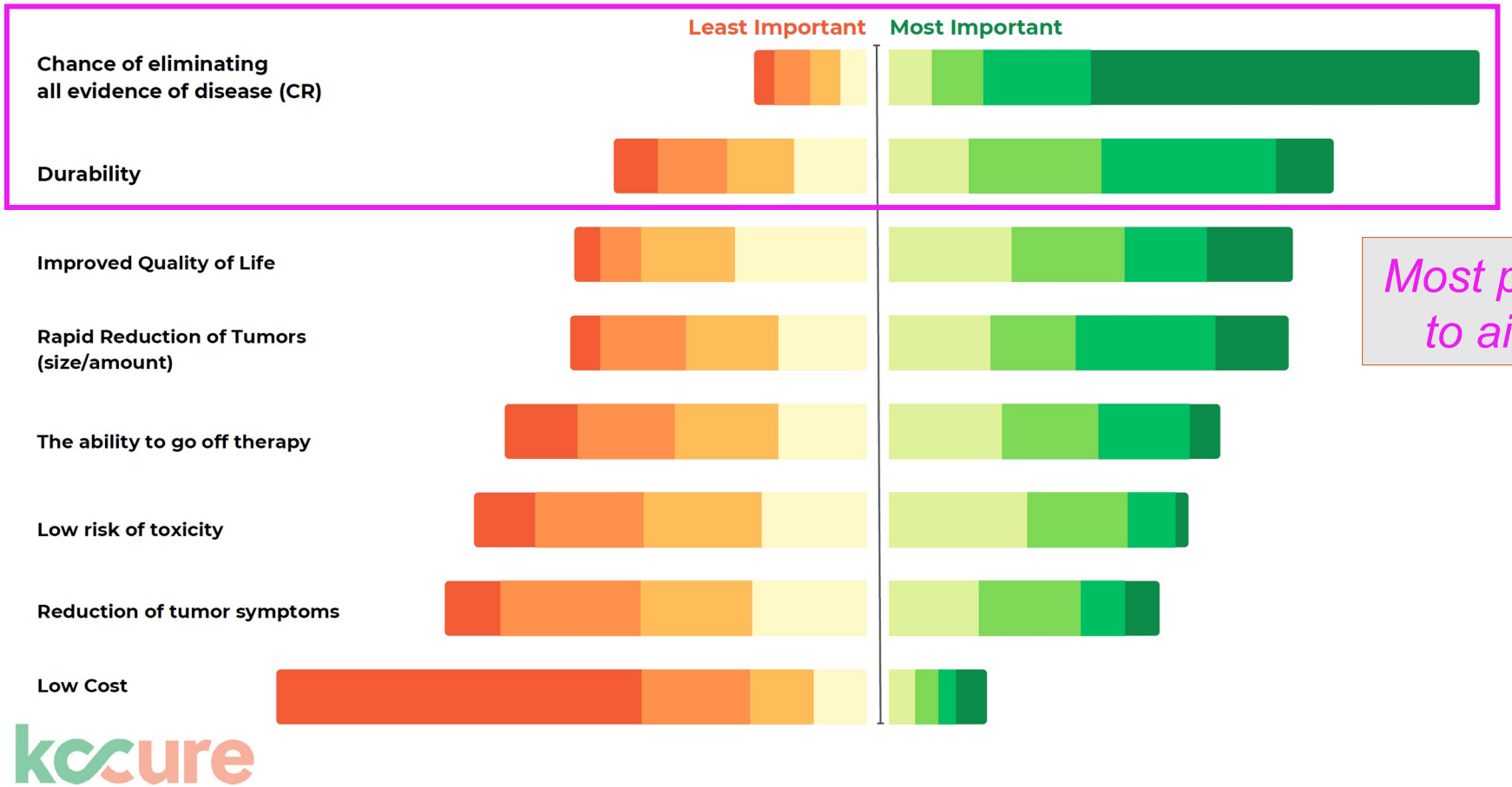
Use other IO agents (anti-PD-1 + CTLA-4)



Ipilimumab salvage rate ~4-14% in HCRN GU16-260, OMNIVORE, and TITAN-RCC

TiNivo-2 figure from UroToday.com; Atkins, J Clin Oncol, 2022; Grimm, Ann Oncol, 2019; McKay, J Clin Oncol, 2020.

What's next? Patient perspective on goals of systemic therapy for advanced RCC

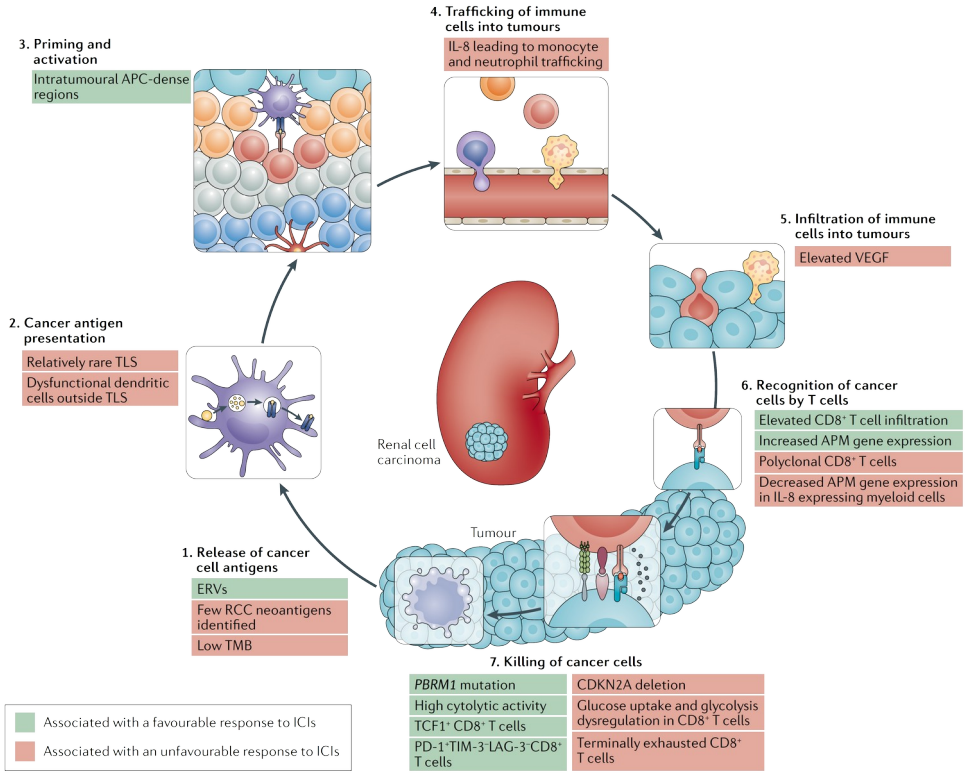


*Most patients want to aim for **cure***

Battle, ASCO 2023.

Novel therapeutic approaches in RCC: aiming for cure

Requires understanding of RCC immunobiology



Braun, Nat Rev Clin Oncol, 2021.

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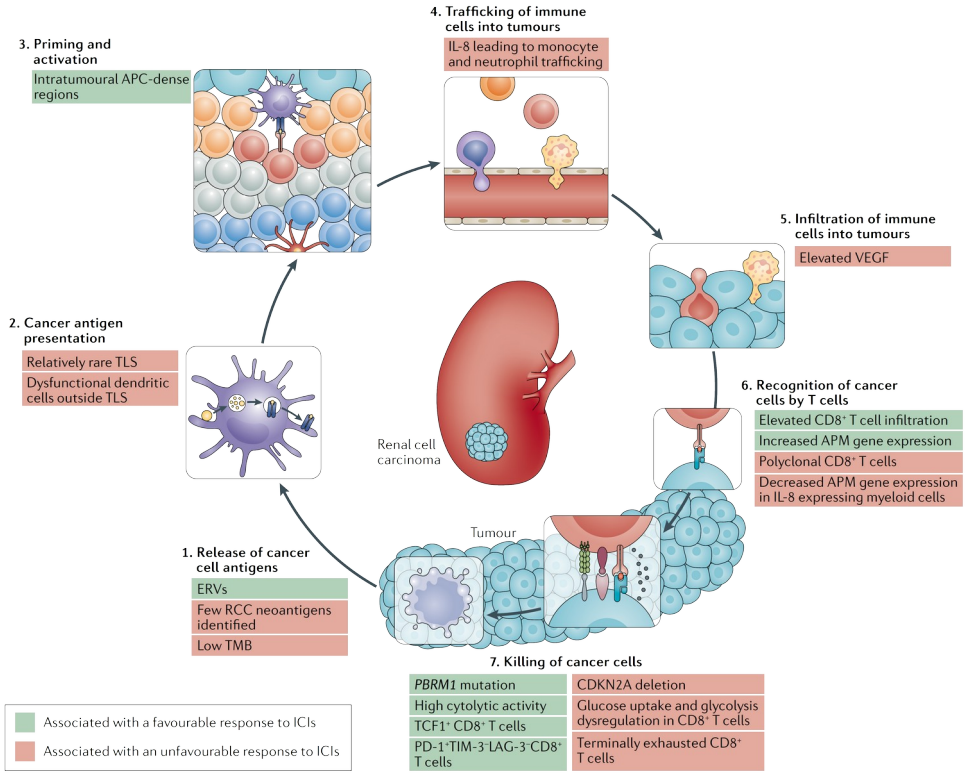
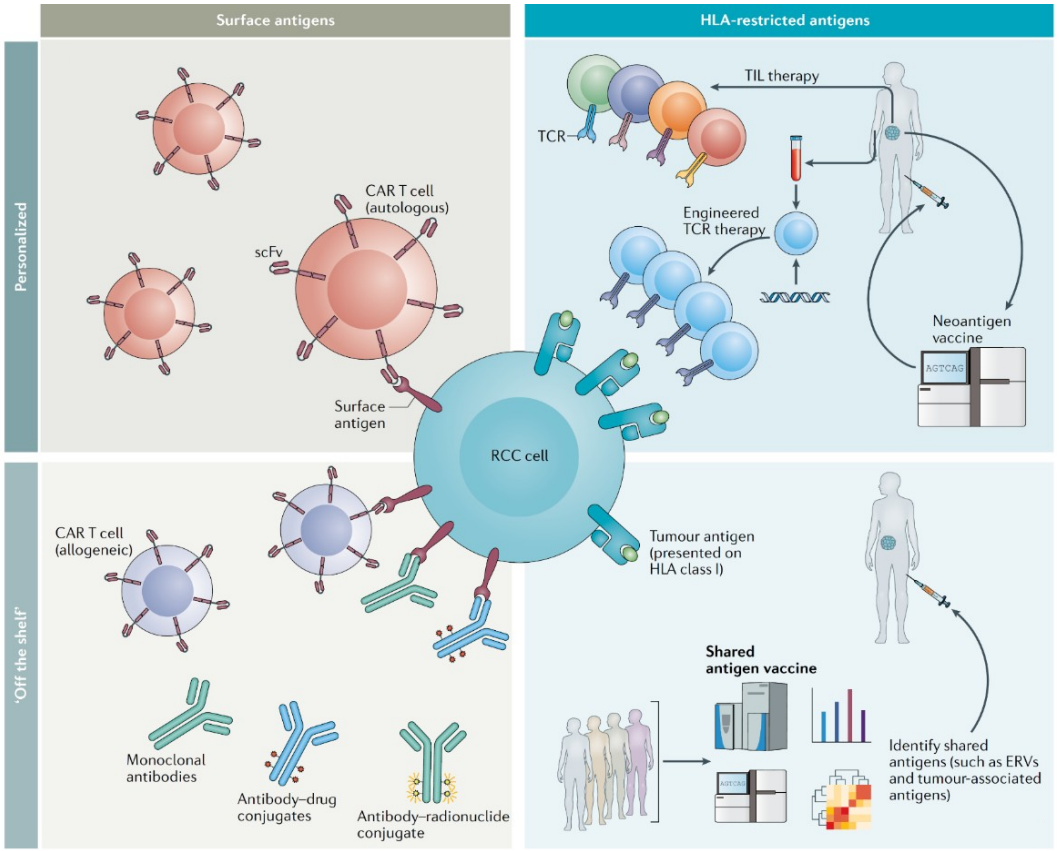


Antigen-specific approaches as a next generation IO



Braun, Nat Rev Clin Oncol, 2021.

Conclusions/Take-Away II

- **Does CONTACT-03 change practice?**
  Yes. Anti-PD-(L)1 should not be used after progression on prior PD-(L)1 (at least until TiNivo-2)
  - More toxicity
  - Potential to compromise dosing of TKI

Conclusions/Take-Away II

- **Does CONTACT-03 change practice?**
  Yes. Anti-PD-(L)1 should not be used after progression on prior PD-(L)1 (at least until TiNivo-2)
  - More toxicity
  - Potential to compromise dosing of TKI

- **Next steps:**
  - *Trials to optimize clinical outcomes (↑ORR, PFS, OS)*
  - *Novel targets – aim for cure*
  - *ALWAYS: listen to the patient perspective*

Acknowledgments

- **Patients and their families**

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  - Dr. Toni Choueiri

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  - Dr. Manojkumar Bupathi

- Dr. Rana McKay
- Dr. David McDermott

- **#ASCO23 organizers, program committee, and staff**

Questions, comments, or interested in collaborating?
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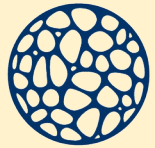

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