Should Everyone Receive Adjuvant Therapy after Resection of High-Risk RCC? No

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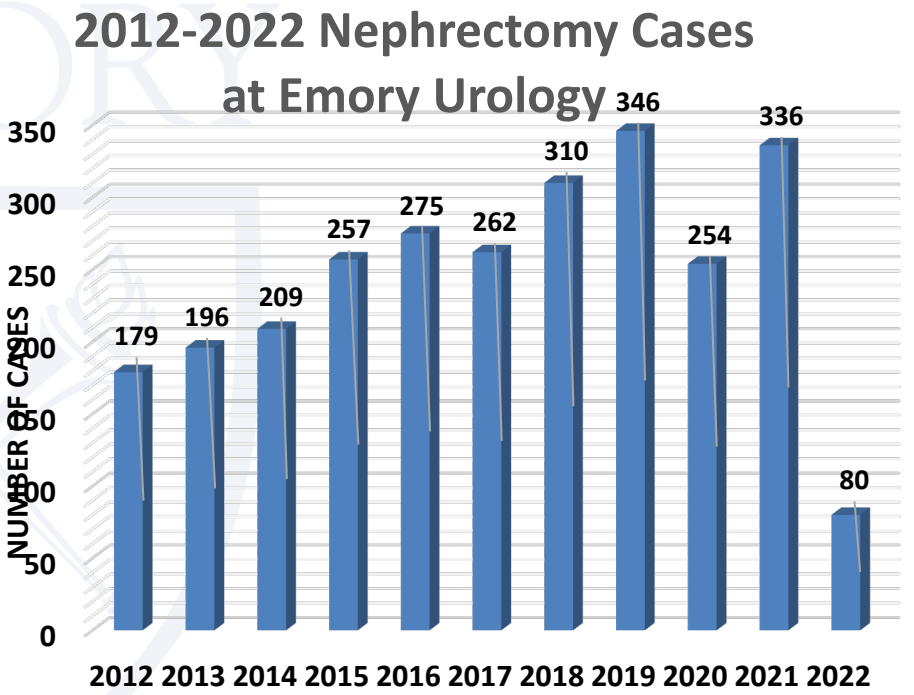
We see these patients…a lot of them

- Certainly not every RCC patient needs adjuvant therapy
- Probably not most of the patients enrolled in current adjuvant studies



~ 35-40% are Stage III

Take home messages

- Tyrosine kinase inhibitors don’t work
- 3 out of 4 PD/PD-L1 trials are negative
- The single positive trial data are immature to change practice
- The signal we see is mostly driven by M1 NED
- The tools we have for predicting progression are poor

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RCC Adjuvant TKI therapy Trials

Study Name	Sponsor	N	Design	Outcome Measure	Status
ASSURE	ECOG/NCI	1941	1 yr sorafenib vs 1 yr sunitinib vs placebo	Relapse free survival	Accrual complete
SORCE	MRC(UK)	1656	3 yrs sorafenib vs 1 yr sorafenib vs placebo	Relapse free survival	Accrual complete
S-TRAC	**Pharma**	**720**	**1 yr sunitinib vs 1 yr placebo**	**Relapse free survival**	**Accrual complete**
PROTECT	Pharma	1500	1 yr pazopanib vs 1 yr placebo	Relapse free survival	Accrual complete
EVEREST	SWOG	1218	1 yr everolimus vs 1 yr placebo	Relapse free survival	Accrual complete
ATLAS	Pharma	592	1 yr axitinib vs 1 yr placebo	Relapse free survival	Accrual complete

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available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Kidney Cancer

Adjuvant Vascular Endothelial Growth Factor–targeted Therapy in Renal Cell Carcinoma: A Systematic Review and Pooled Analysis

Maxine Sun [a], Lorenzo Marconi [b], Tim Eisen [c], Bernard Escudier [d], Rachel H. Giles [e,f], Naomi B. Haas [g], Lauren C. Harshman [a], David I. Quinn [h], James Larkin [i], Sumanta K. Pal [j], Thomas Powles [k], Christopher W. Ryan [l], Cora N. Sternberg [m], Robert Uzzo [n], Toni K. Choueiri [a,1,], Axel Bex [o,1,*]*

- 3 randomized phase 3 studies, ASSURE (n=1943), S-TRAC (n=615), PROTECT (n=1135).
- **Pooled analysis: VEGF TKI was not associated with improved DFS (HR: 0.92 0.83-1.03, p: 0.16).**
- VEGF TKI associated with higher grade 3-4 AEs (OR: **5.89**, p<0.001).

Sun M, Eur Urol 2018

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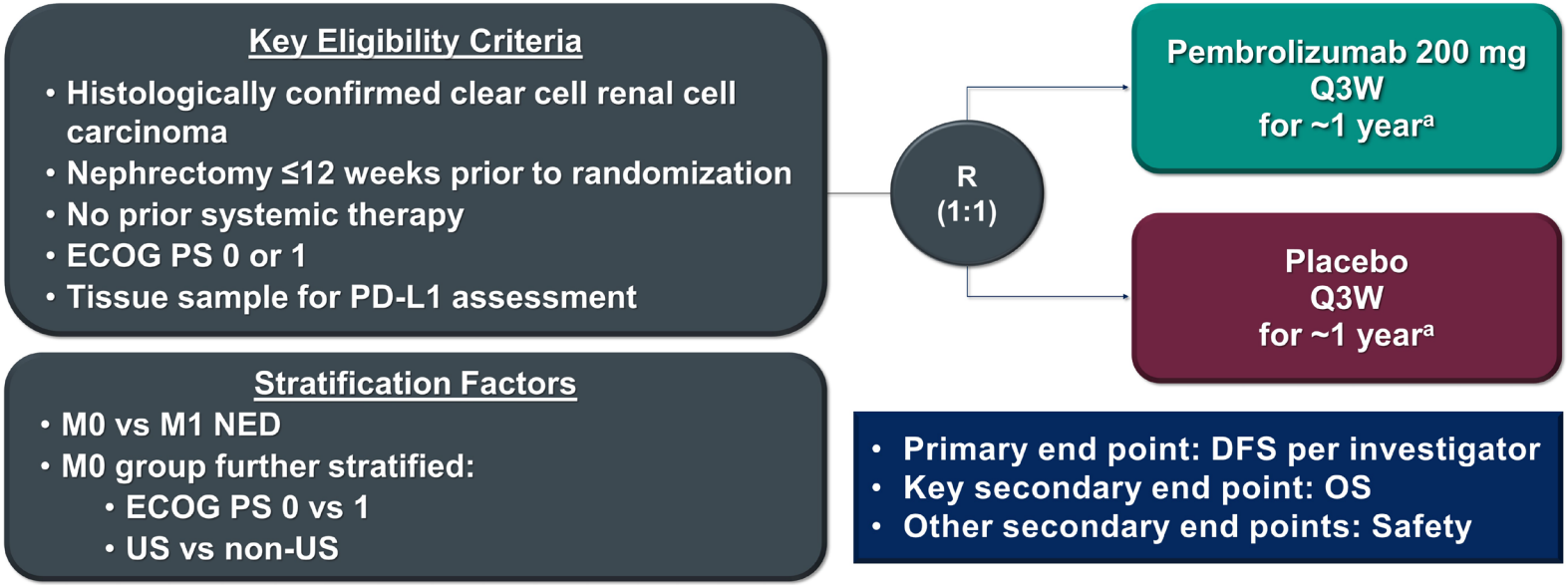
Immune agents (IO) to the rescue…?

RCC Adjuvant IO trials

Study Name	Drugs	1° Endpoint	Status
Immotion 010 (n=778)	Atezo vs Placebo	DFS	NEGATIVE*
Checkmate914 (n=1600)	Nivo/Ipi vs Placebo	DFS	NEGATIVE*
ECOG 8134/Prosper (n=805)	Neoadjuvant nivolumab → surgery → adjuvant nivolumab vs observation	RFS	NEGATIVE
RAMPART (n=1750)	Durvalumab vs. Durvalumab+Tremelimumab vs. Surveillance	DFS and OS	Currently Accruing
KEYNOTE 564 (n=994)	**Pembrolizumab vs Placebo**	**DFS**	**Positive**

Adjuvant Pembrolizumab vs. Placebo n=994

KEYNOTE-564 Study Design

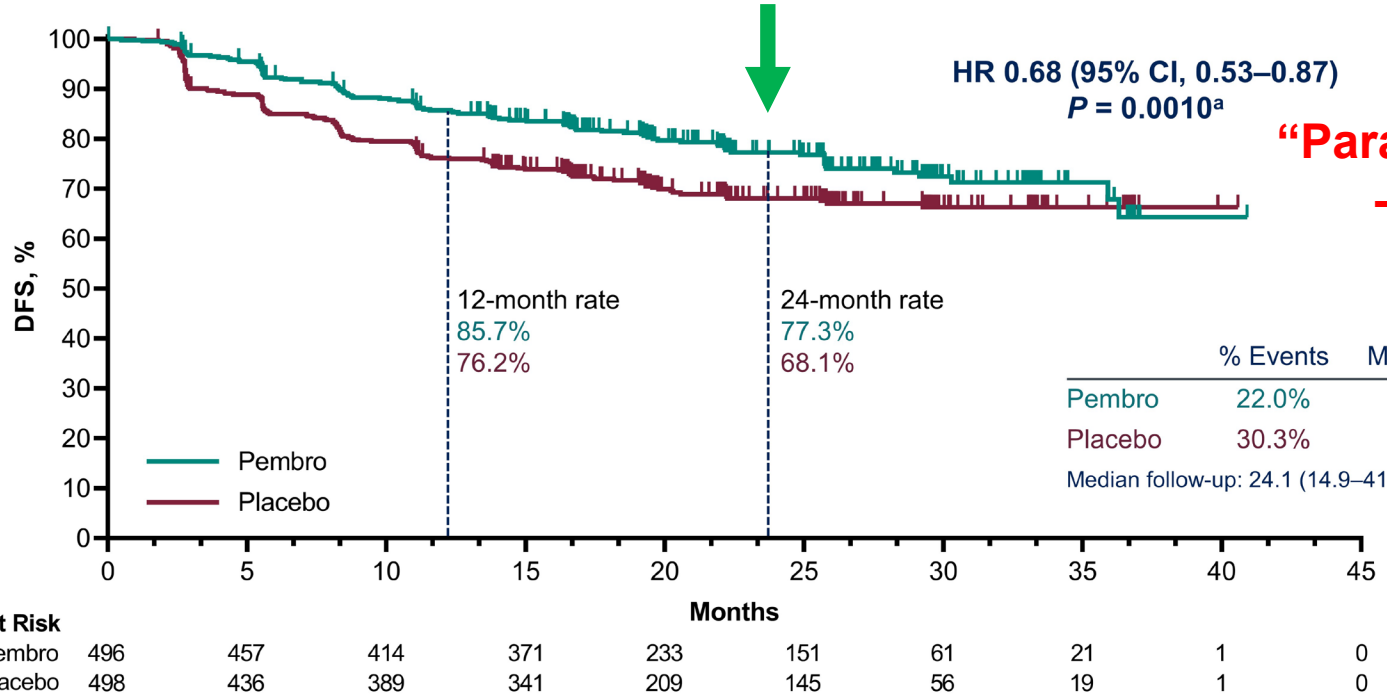


DFS, disease-free survival; Q3W, every 3 weeks.
[a]≤17 cycles of treatment were equivalent to ~1 year.

DFS by Investigator, ITT Population

"game-changing"
-Twitter

"Paradigm shift"
-ASCO Post



	% Events	Median (95% CI)
Pembro	22.0%	NR (NR–NR)
Placebo	30.3%	NR (NR–NR)

Median follow-up: 24.1 (14.9–41.5) months.

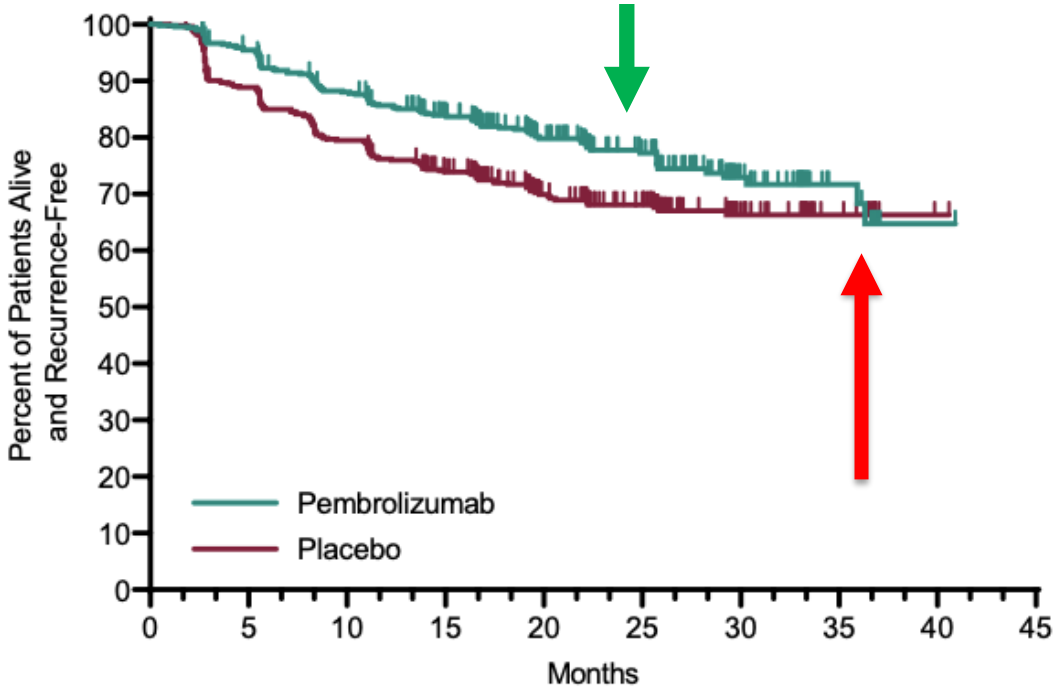
No. at Risk										
Pembro	496	457	414	371	233	151	61	21	1	0
Placebo	498	436	389	341	209	145	56	19	1	0

[a]Crossed prespecified p-value boundary for statistical significance of 0.0114.
ITT population included all randomized participants. NR, not reached. Data cutoff date: December 14, 2020.

Choueiri T, NEJM 2021

Looking under the hood

Disease-Free Survival by Investigator, Intention-to-Treat Population, what about @ 36 months?



No. at Risk										
Pembrolizumab	496	456	413	370	232	151	61	21	1	0
Placebo	498	436	389	341	209	145	56	19	1	0

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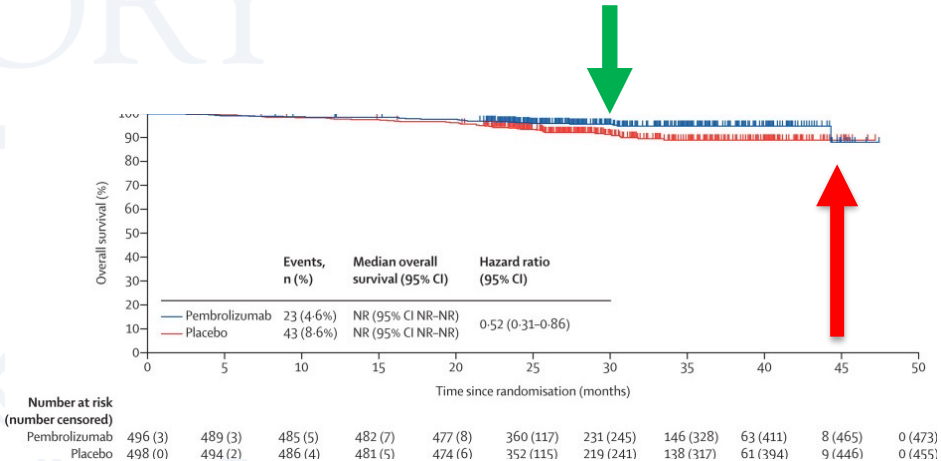
6 more months of followup, not much has changed from the first interim analysis

- “requested by the regulatory authorities” – quote from the paper
- Only 33% of the 200 events needed for final analysis have occurred (*this is because of poorly selected pts who were not likely to recur*)



Powles T, Lancet Oncol 2022

Which patients were in the Keynote 564 trial? Disease categories

Intermediate – High Risk		High Risk for Recurrence		M1 NED
pT2	pT3	pT4	pT any	NED after resection of oligomets (including synchronous)
Grade 4 or sarcomatoid	Any Grade	Any grade	Any grade	
N0	N0	N0	N1	≤1 year from NT
M0	M0	M0	M0	

% in each of these Disease Categories

Intermediate –High Risk		High Risk		M1 NED
PT2	pT3	pT4	pT any	NED after resect of oligomets
Grade 4 or sarc	Any Grade	Any grade	Any grade	
N0	N0	N0	N1	≤1 year from NT
M0	M0	M0	M0	
86%		**8%**		**6%**

34.6% of patients were low-grade (1 or 2)!

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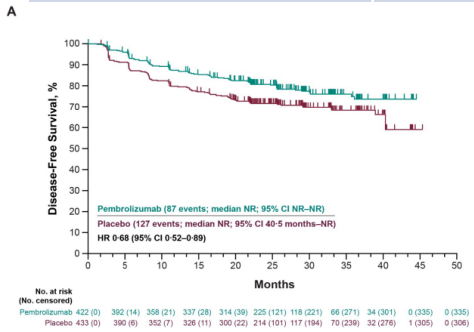
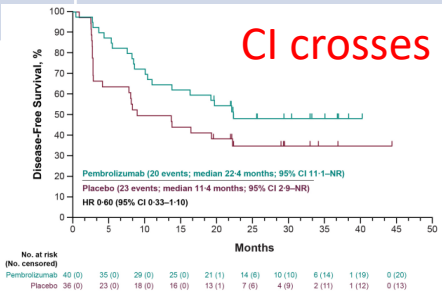
% in each of these Disease Categories

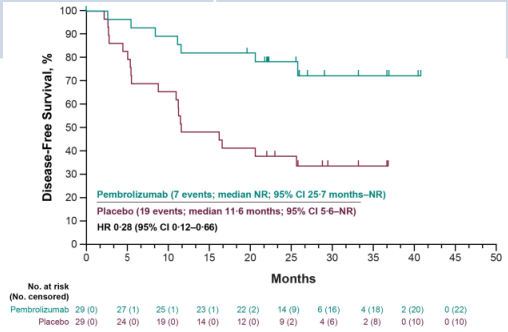
Intermediate –High Risk		High Risk		M1 NED
PT2	pT3	pT4	pT any	NED after resect of oligomets
Grade 4 or sarc	Any Grade	Any grade	Any grade	
N0	N0	N0	N1	≤1 year from NT
M0	M0	M0	M0	
86%		**8%**		**6%**



If really a class effect, should be true for both groups



CI crosses 1



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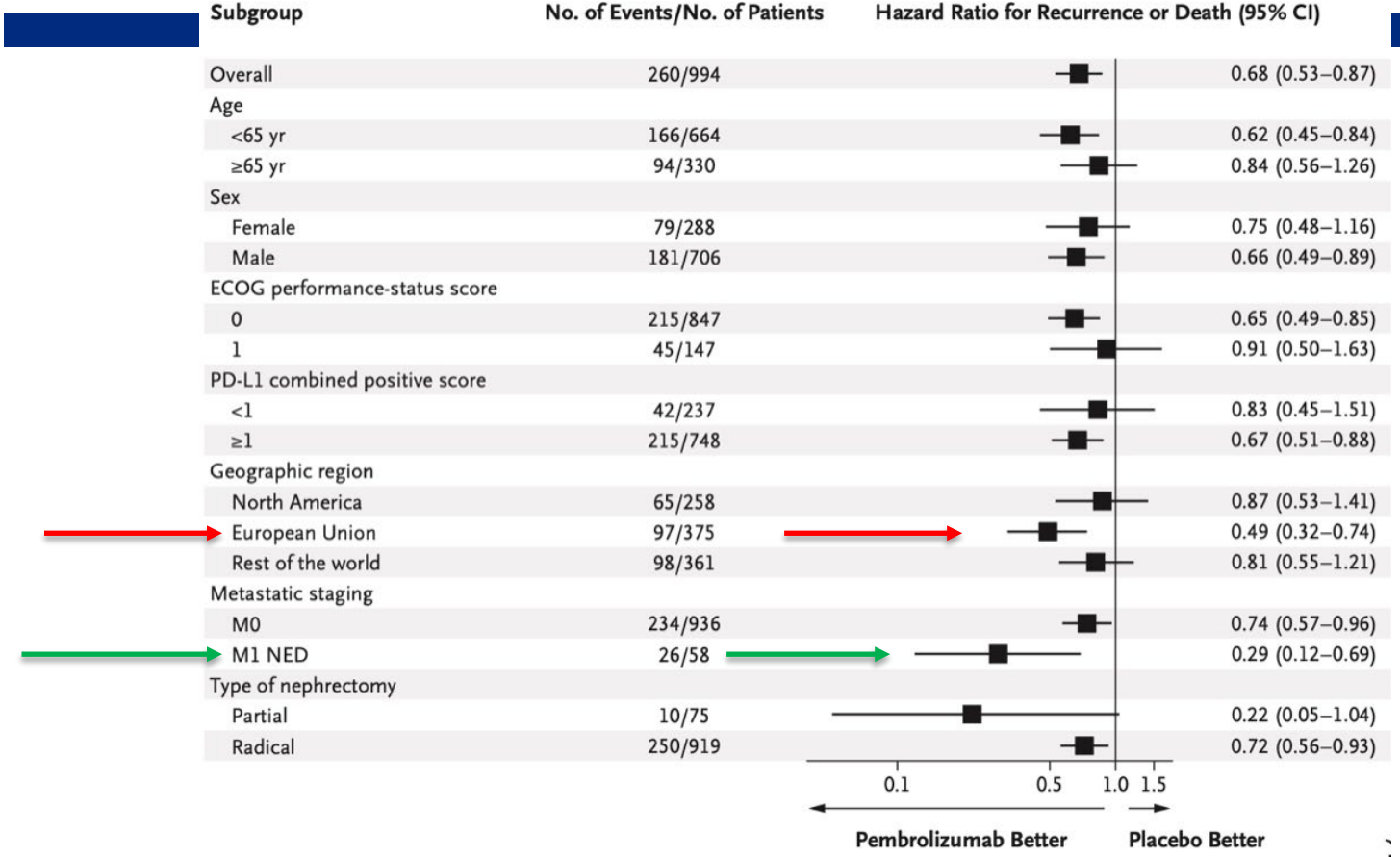
DFS by investigator, Subgroups, IIT population



Adverse Events/Immune-Mediated Adverse Events (iAE)

These are real (and the patient may not have disease)

- Any Grade iAE 35%
- Grade 3-4 iAE's in Pembro 8.6% vs. 0.6% in Placebo
- Discontinuation for AE 21% (vs. 2% in placebo)
- 2 Deaths in pembro group*
- Colitis
- Adrenal Insufficiency
- Pneumonitis
- Hepatitis
- Skin
- Thyroiditis

Patients with one or more events—no. (%)	Pembrolizumab N = 488		Placebo N = 496	
	Any Grade	Grade 3-4†	Any Grade	Grade 3-4†
Any immune-mediated adverse event‡¶	169 (34.6)	42 (8.6)	29 (5.8)	3 (0.6)
Adrenal insufficiency	10 (2.0)	6 (1.2)	1 (0.2)	1 (0.2)
Colitis	8 (1.6)	5 (1.0)	1 (0.2)	0
Encephalitis	1 (0.2)	1 (0.2)	0	0
Hepatitis	5 (1.0)	4 (0.8)	0	0
Hyperthyroidism	58 (11.9)	1 (0.2)	1 (0.2)	0
Hypophysitis	2 (0.4)	2 (0.4)	0	0
Hypothyroidism	103 (21.1)	1 (0.2)	18 (3.6)	0
Myasthenic syndrome	3 (0.6)	0	0	0
Myocarditis	1 (0.2)	1 (0.2)	0	0
Myositis	2 (0.4)	0	1 (0.2)	0
Nephritis	3 (0.6)	1 (0.2)	0	0
Pneumonitis	11 (2.3)	4 (0.8)	5 (1.0)	0
Sarcoidosis	4 (0.8)	0	0	0
Severe skin reaction	8 (1.6)	8 (1.6)	2 (0.4)	2 (0.4)
Thyroiditis	6 (1.2)	2 (0.4)	1 (0.2)	0
Type 1 diabetes mellitus	9 (1.8)	9 (1.8)	0	0
Uveitis	0	0	1 (0.2)	0
Vasculitis	2 (0.4)	1 (0.2)	0	0

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Restricted mean disease-free survival times

-Are they actually that different? I don't think so

- DFS
  Pembro 20.97 months vs.
  Placebo 19.11 months
  (1.86 mo, 95% CI 0.95-2.77)

- OS
  Pembro 23.66 months vs.
  Placebo 23.47 months
  (0.19 mo, 95% CI 0.13 - 0.5)

Table S8A. Restricted Mean Survival Times of Disease-Free Survival Based on Investigator Assessment, Intention-to-Treat Population.*

Follow-up Duration	Pembrolizumab N = 496		Placebo N = 498		Difference (95% CI) vs Placebo
	No. Events	RMST	No. Events	RMST	
12 months	68	11.19	117	10.49	0.71 (0.36 to 1.05)
18 months	86	16.21	136	14.94	1.28 (0.66 to 1.89)
24 months	98	20.97	148	19.11	1.86 (0.95 to 2.77)

Table S8B. Restricted Mean Survival Times of Overall Survival Assessment, Intention-to-Treat Population.*

Follow-up Duration	Pembrolizumab N = 496		Placebo N = 498		Difference (95% CI) vs Placebo
	No. Events	RMST	No. Events	RMST	
12 months	7	11.91	10	11.91	0.01 (−0.10 to 0.11)
18 months	10	17.82	16	17.75	0.08 (−0.12 to 0.27)
24 months	14	23.66	26	23.47	0.19 (−0.13 to 0.50)

Investigator Assessment, ITT population

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Just who are the ccRCC patients who develop recurrence? Who should get adjuvant IO therapy?

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What is the real risk of recurrence?

- N=3633 patients
- 75% ccRCC
- Models for each histology
- C-Index for ccRCC
  - 0.83 PFS,
  - 0.86 CSS

	Progression				Death from RCC			
Feature	HR	95% CI	p value	Points	HR	95% CI	p value	Points
Age at surgery (yr)								
<60					Reference			0
>60					1.41	1.19–1.68	<0.01	1
ECOG status								
0					Reference			0
>1					1.62	1.29–2.05	<0.01	2
Constitutional symptoms								
No	Reference			0	Reference			0
Yes	1.23	1.05–1.44	<0.01	1	1.27	1.06–1.52	<0.01	1
Adrenalectomy								
No					Reference			0
Yes					1.34	1.13–1.60	<0.01	1
Surgical margins								
Negative					Reference			0
Positive					1.63	1.11–2.39	0.01	1
Grade								
1	Reference			0	Reference			0
2	1.82	1.17–2.82	<0.01	2	1.76	1.01–3.06	0.047	2
3	2.80	1.79–4.37	<0.01	3	3.07	1.76–5.35	<0.01	3
4	3.22	1.93–5.38	<0.01	3	3.86	2.07–7.21	<0.01	4
Coagulative necrosis								
No	Reference			0	Reference			0
Yes	1.93	1.63–2.29	<0.01	2	2.15	1.76–2.63	<0.01	2
Sarcomatoid differentiation								
No	Reference			0	Reference			0
Yes	2.15	1.54–3.01	<0.01	2	2.47	1.74–3.53	<0.01	3
Tumor size (cm)								
≤4	Reference			0	Reference			0
>4 to ≤7	2.95	2.27–3.83	<0.01	3	3.91	2.68–5.70	<0.01	4
>7 to ≤10	3.74	2.85–4.92	<0.01	4	4.30	2.91–6.36	<0.01	4
>10	3.82	2.84–5.14	<0.01	4	5.16	3.43–7.76	<0.01	5
Perinephric or renal sinus fat invasion								
No	Reference			0	Reference			0
Yes	1.58	1.33–1.88	<0.01	1	1.63	1.35–1.97	<0.01	2
Tumor thrombus								
No	Reference			0	Reference			0
Level 0	1.25	1.25–1.51	0.02	1	1.15	0.93–1.43	0.20	0
Level 1–4	1.74	1.41–2.15	<0.01	2	1.49	1.16–1.90	<0.01	1
Extension beyond kidney								
No	Reference			0				
Yes	1.86	1.27–2.70	<0.01	2				
Nodal involvement								
No nodal dissection	Reference			0	Reference			0
No	1.16	0.99–1.37	0.07	0	1.05	0.87–1.26	0.63	0
Yes	2.31	1.78–2.99	<0.01	2	1.66	1.26–2.20	<0.01	2

Leibovich BC et al Eur Urol 2018

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What is the real risk of recurrence?

	Progression-free survival (95% CI)		
	N (%)	5 yr	10 yr
ccRCC score			
0	118 (4)	98 (97–98)	97 (96–97)
1	21 (1)	97 (96–97)	95 (95–96)
2	489 (19)	95 (94–96)	93 (92–95)
3	296 (11)	93 (92–94)	91 (89–92)
4	69 (3)	91 (89–92)	87 (85–89)
5	332 (13)	87 (85–88)	82 (81–83)
6	307 (12)	82 (80–84)	76 (74–77)
7	204 (8)	75 (72–77)	67 (65–69)
8	167 (6)	66 (63–69)	57 (54–60)
9	165 (6)	56 (52–59)	45 (42–47)
10	127 (5)	44 (40–47)	32 (27–36)
11	119 (5)	31 (26–35)	20 (15–24)
12	97 (4)	19 (15–22)	10 (6–14)
13	60 (2)	9 (7–11)	4 (2–5)
14	27 (1)	3 (1–5)	1 (0–2)
>15[a]	31 (1)	1 (0–1)	0 (0–0)

	Progression				Death from RCC			
Feature	HR	95% CI	*p* value	Points	HR	95% CI	*p* value	Points
Age at surgery (yr)								
<60					Reference			0
>60					1.41	1.19–1.68	<0.01	1
ECOG status								
0					Reference			0
>1					1.62	1.29–2.05	<0.01	2
Constitutional symptoms								
No	Reference			0	Reference			0
Yes	1.23	1.05–1.44	<0.01	1	1.27	1.06–1.52	<0.01	1
Adrenalectomy								
No					Reference			0
Yes					1.34	1.13–1.60	<0.01	1
Surgical margins								
Negative					Reference			0
Positive					1.63	1.11–2.39	0.01	1
Grade								
1	Reference			0	Reference			0
2	1.82	1.17–2.82	<0.01	2	1.76	1.01–3.06	0.047	2
3	2.80	1.79–4.37	<0.01	3	3.07	1.76–5.35	<0.01	3
4	3.22	1.93–5.38	<0.01	3	3.86	2.07–7.21	<0.01	4
Coagulative necrosis								
No	Reference			0	Reference			0
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Perinephric or renal sinus fat invasion								
No	Reference			0	Reference			0
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Tumor thrombus								
No	Reference			0	Reference			0
Level 0	1.25	1.25–1.51	0.02	1	1.15	0.93–1.43	0.20	0
Level 1–4	1.74	1.41–2.15	<0.01	2	1.49	1.16–1.90	<0.01	1
Extension beyond kidney								
No	Reference			0				
Yes	1.86	1.27–2.70	<0.01	2				
Nodal involvement								
No nodal dissection	Reference			0	Reference			0
No	1.16	0.99–1.37	0.07	0	1.05	0.87–1.26	0.63	0
Yes	2.31	1.78–2.99	<0.01	2	1.66	1.26–2.20	<0.01	2

Leibovich BC et al Eur Urol 2018

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More real world data from Emory

Table 1: Progression free survival estimates for ccRCC (n=1717) by Leibovich 2018 risk score for entire Emory cohort (n=2,295)

		Progression Free Survival (% [95% CI])		
	Risk Score	n (%)	5 Years	10 Years
ccRCC	0	34 (2)	97 (79-100)	97 (79-100)
	1	6 (0.3)*	100 (100-100)	100 (100-100)
	2	283 (16.5)	94 (90-97)	91 (84-95)
	3	285 (16.6)	96 (91-98)	91 (82-96)
	4	126 (7.3)	92 (85-96)	86 (66-95)
	5	132 (7.7)	94 (85-97)	82 (65-91)
	6	187 (10.9)	89 (81-93)	85 (75-91)
	7	112 (6.5)	86 (75-93)	58 (30-78)
	8	119 (6.9)	69 (57-79)	66 (52-76)
	9	88 (5.1)	79 (65-88)	58 (26-80)
	10	67 (3.9)	69 (53-81)	55 (35-71)
	11	59 (3.4)	45 (27-62)	40 (21-58)
	12	60 (3.5)	43 (26-59)	30 (13-50)
	13	38 (2.2)	51 (30-69)	51 (30-69)
	14	50 (2.9)	59 (40-73)	40 (17-63)
	≥15	70 (4.1)	44 (28-60)	44 (28-60)

*Low sample size (<15) at respective score limiting analysis. Abbreviations: Clear cell renal cell carcinoma (ccRCC); Progression Free Survival (PFS).

Table 2: Progression free survival estimates for pRCC (n=402) and chRCC (177) by Leibovich 2018 risk score for entire Emory cohort (n=2,295)

		Progression Free Survival (% [95% CI])		
	Risk Score	n (%)	5 Years	10 Years
pRCC	1	153 (38.8)	94 (88-97)	89 (80-95)
	2	204 (51.8)	94 (88-97)	89 (77-94)
	3	37 (9.4)	43 (22-63)	29 (10-51)
chRCC	1	164 (92.7)	96 (90-98)	88 (75-94)
	2	10 (5.6)**	75 (13-96)	75 (13-96)
	3*	3 (1.7)	-	-

*Patients lost to follow-up and were censored, so unable to accurately determine frequencies. **Low sample size (<15) at respective score limiting analysis. Abbreviations: Papillary renal cell carcinoma (pRCC); Chromophobe renal cell carcinoma (chRCC); Progression Free Survival (PFS).

- N=2,295 patients; 75% ccRCC
- ccRCC / pRCC / chRCC AUC:
  - 5-yr PFS 0.81 / 0.74 / 0.66
  - 10-yr PFS 0.78/ 0.71 / 0.55

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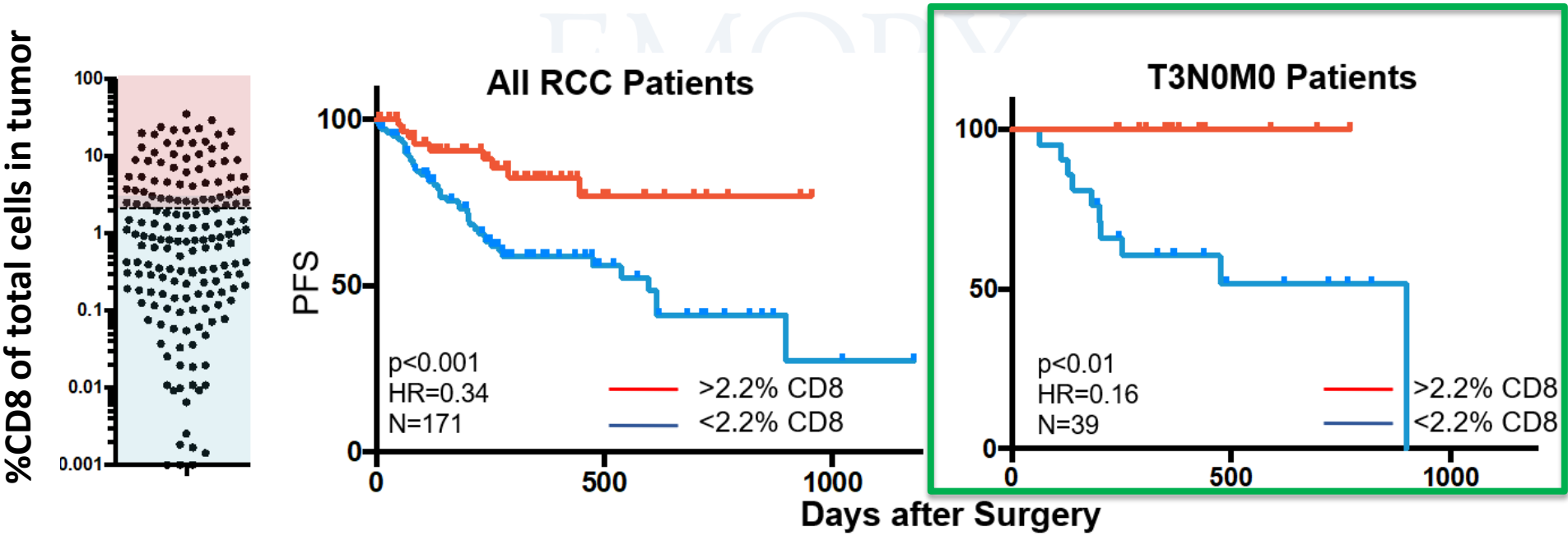
Disease Categories – Risk of recurrence
Does this explain Keynote 564 results?

Intermediate –High Risk		High Risk		M1 NED
PT2	pT3	pT4	pT any	NED after resect of oligomets ≤1 year from NT
Grade 4 or sarc	Any Grade	Any grade	Any grade	
N0	N0	N0	N1	
M0	M0	M0	M0	
86%		8%	6%	
Leibovich/MayoPFS nomogram -5yr DFS				
75%	56%	56%	56%	n/a
ASSURE DFS nomogram -2yr DFS				
96.4%	80%	n/a	58.5%	n/a

Translational science may inform us about patient selection

CD8 T-cell infiltration predicts progression free survival after surgery in renal cell carcinoma patients



Stay tuned for validation, thanks to DOD TRP grant

Jansen, Prokhnevska, Master…Kissick, Nature, 2019

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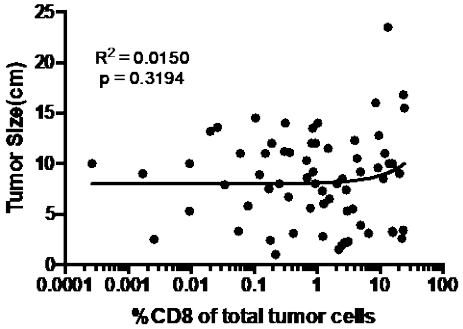
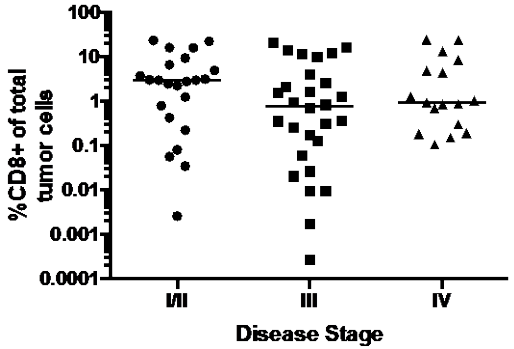
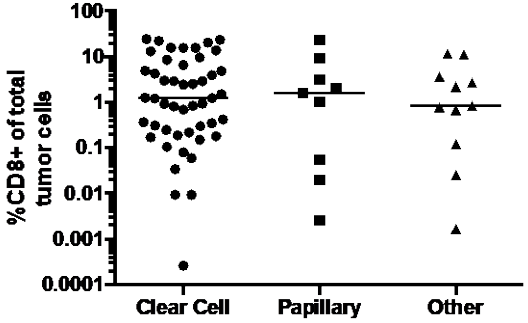
CD8 T cell response is independent of tumor size, stage, subtype and demographic factors







Courtesy, Dr. Carey Jansen

Jansen et al, *Nature*, 2019

Conclusions

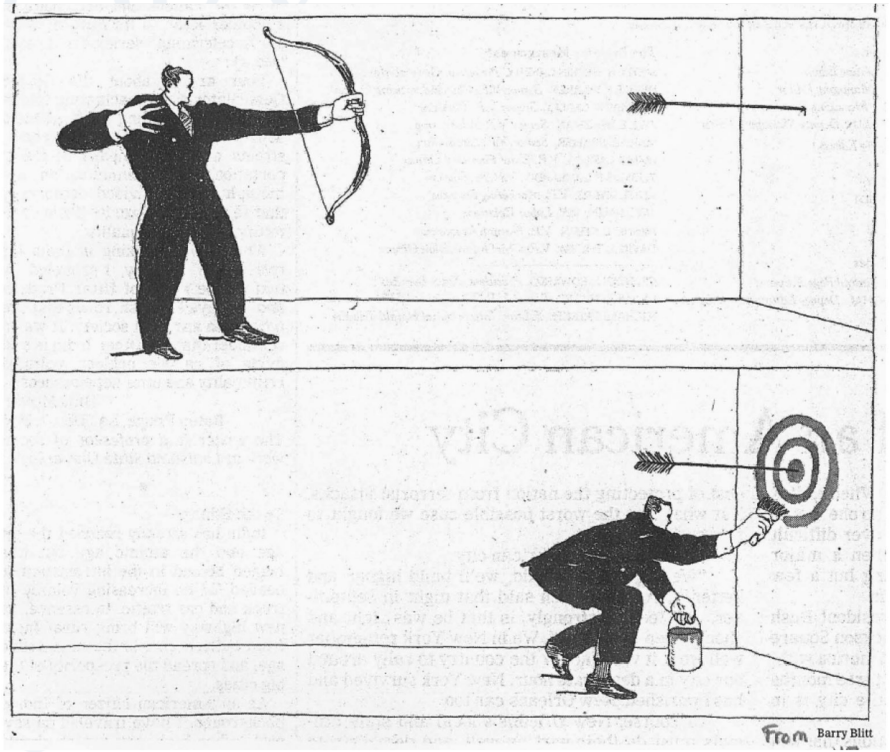
- Expensive, not easy to tolerate, data immature
- Can we find the right patients to treat based on current pathologic features: NO

- Maybe just for patients who are:
  - *pM1 NED s/p metastatectomy*

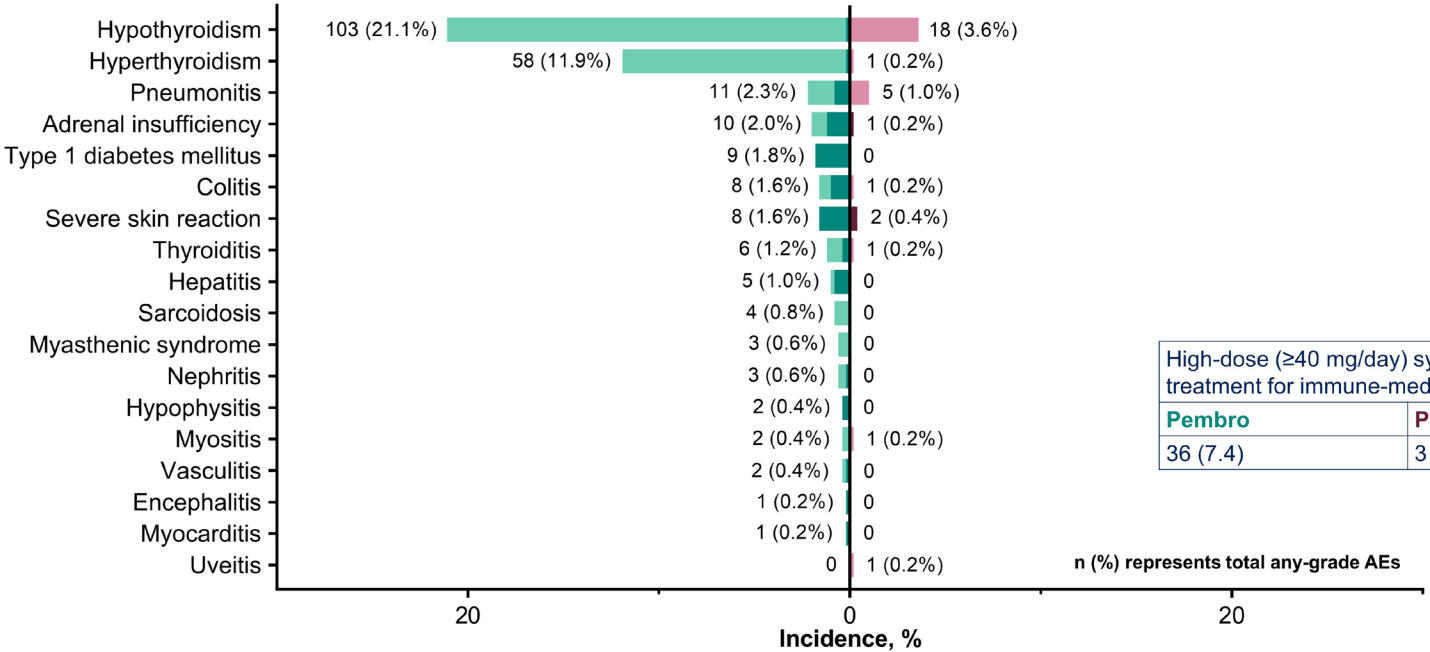
EMORY

Thank you!

- vmaster@emory.edu
- 404-217-6419



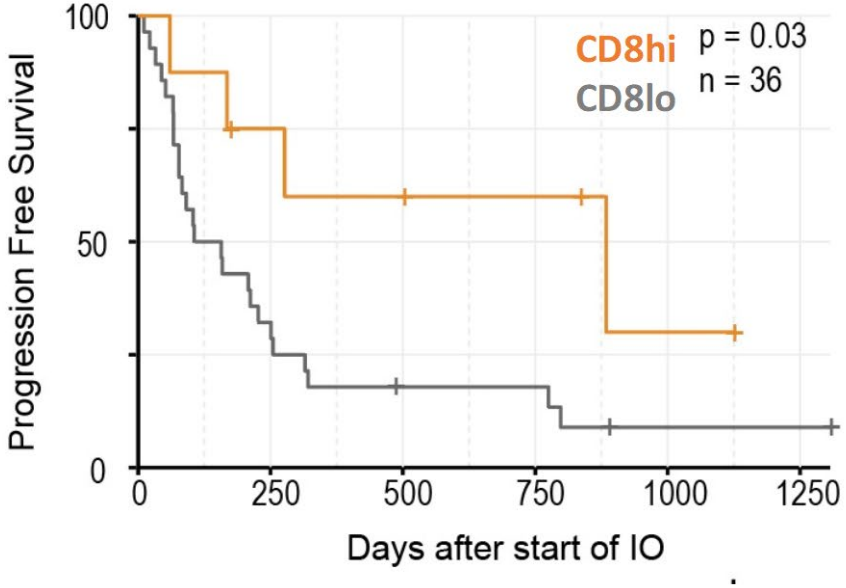
Immune-Mediated AEs[a], As-Treated Population

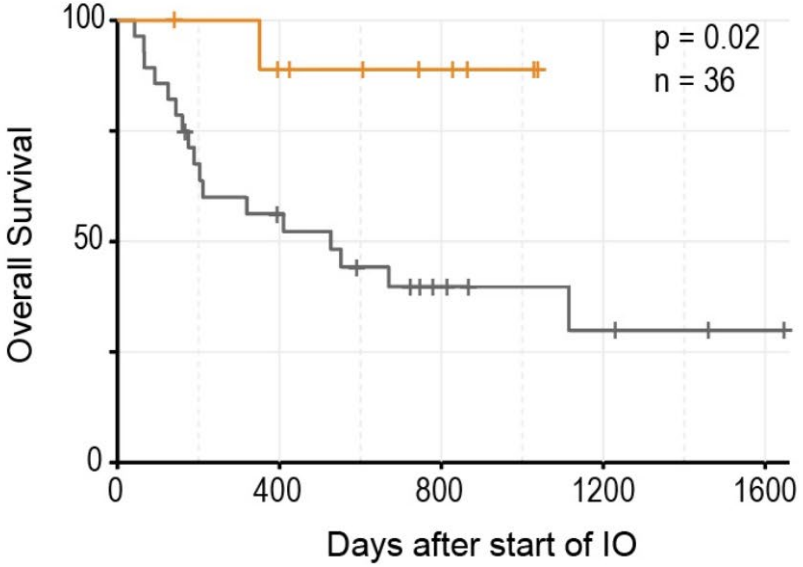


High-dose (≥40 mg/day) systemic corticosteroid treatment for immune-mediated AEs, n (%)	
Pembro	**Placebo**
36 (7.4)	3 (0.6)

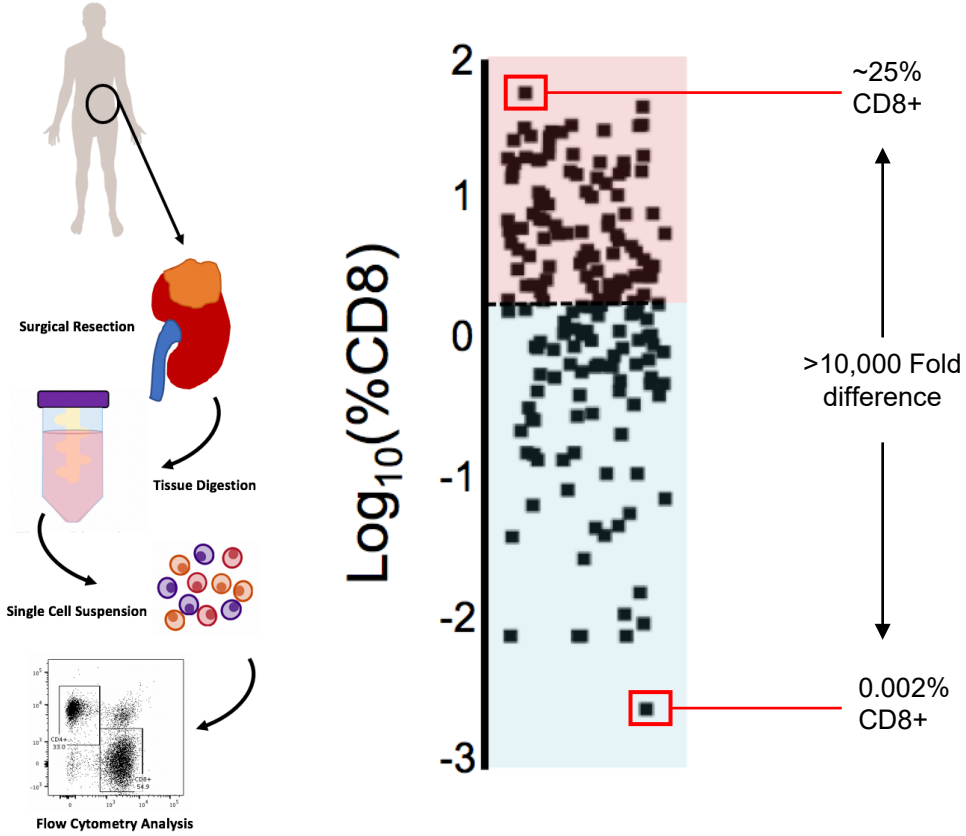
[a]Based on a prespecified list of terms included regardless of attribution to study treatment by investigator.
Infusion reactions, pembro: any grade in 7 participants (1.4%), grade 3 in 2 participants (0.4%). Infusion reactions, placebo: any grade in 5 participants (1.0%), grade 3-4 in no participants. No deaths due to immune-mediated events occurred. As-treated population included all participants who received ≥1 dose of study treatment. Data cutoff date: December 14, 2020.

Response to checkpoint therapy is associated with CD8 T cells in the tumor at the time of surgery





CD8 T-cell infiltration predicts progression in RCC



Jansen et al, *Nature*, 2019

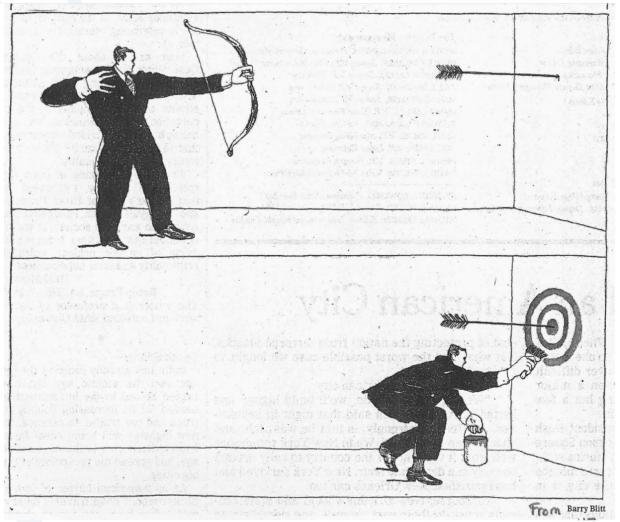
Keynote 564 – Updated 30 month analysis ASCO GU 2022

- DFS benefit with pembrolizumab was maintained (HR 0.63, 95% CI 0.50−0.80; nominal P < 0.0001)
- Consistent across subgroups,
- M0 disease with intermediate-high risk of recurrence (HR 0.68, 95% CI 0.52−0.89),
- M0 high risk of recurrence (HR 0.60, 95% CI 0.33−1.10)
- M1 NED (HR 0.28, 95% CI 0.12−0.66).

- The estimated DFS rate at 24 months was 78.3% with pembrolizumab vs 67.3% with placebo.
- OS (HR 0.52, 95% CI 0.31−0.86; P = 0.0048);
- p-value did not cross the statistical hypothesis testing boundary and additional follow-up is planned for this key secondary endpoint.

EMORY

Conclusions



Not TKI’s for sure

What does the science tell us?