Twitter Thread by Sumanta Pal

Sumanta Pal
@montypal

It's Monday AM post-@ASCO #GU21 & clinic starts in a couple of hours! Lots to process - I'll try to tackle optimal 1L tx for #kidneycancer. I'll make a case for cabo/nivo, leaning on the beautiful (& timely) tables below from @lalaniMD, @SoaresAndrey & @brian_rini (1/15)

Summary of first-line doublet combinations in RCC (at Feb 13, 2021)*

	CHECKMATE 214[1]		KEYNOTE 426[2,3]		CHECKMATE 9ER[4]		CLEAR[5]	
	Ipi / Nivo	Sunitinib	Axi / Pembro	Sunitinib	Cabo / Nivo	Sunitinib	Len / Pembro	Sunitinib
Prognostic groups	Fav 23% / Int 61% / Poor 17% Intermediate/Poor risk groups		Fav 32% / Int 55% / Poor 13% All risk groups		Fav 23% / Int 58% / Poor 19% All risk groups		Fav 31% / Int 60% / Poor 9% All risk groups	
Follow-up, mos	55		30.6		18.1		27	
ORR (%)	42	27	60	40	56	27	71	36
CR	10	1	9	3	8	5	16	4
PR	32	25	51	37	48	23	55	32
SD	31	44	23	35	32	42	19	38
PD	19	17	11	17	6	14	5	14
Median OS, mos	48.1 (35.6-NE)	26.6 (22.1-33.5)	NE	35.7 (33.3-NE)	NE	NE (22.6-NE)	NE (33.6-NE)	NE
OS HR (95%CI)	0.65 (0.54-0.78)		0.68 (0.55-0.85)		0.60 (0.40-0.89)		0.66 (0.49-0.88)	
Median PFS, mos	11.2	8.3	15.4	11.1	16.6	8.3	23.9	9.2
PFS HR (95%CI)	0.74 (0.62-0.88)		0.71 (0.60-0.84)		0.51 (0.41-0.64)		0.39 (0.32-0.49)	

*Includes first line combination data positive for OS. Not intended for cross trial comparisons.

@LalaniMD

1. Albiges L, et al. ESMO Open. 2020;5:e001079. 2.Powles T, et al. Lancet Oncol. 2020;21:1563-73. 3. Rini BI et al. N Engl J Med. 2019;380:1116-27.
4. Choueiri T, et al. ESMO 2020, 6960_PR. 5. Motzer R et al. J Clin Oncol 39, 2021 (suppl 6; abstr 269).

What about IO/IO? We have long f/u w #CM214 data w nivo/ipi, no doubt (@AlbigesL et al in @myESMO Open). And treatment-free interval discussed by McDermott @BIDMChealth is no doubt impt. But we've known data not as impressive for favorable risk (2/15)

Open access Original research

ESMO Open Cancer Horizons

Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial

Laurence Albiges ,[1] Nizar M Tannir,[2] Mauricio Burotto,[3] David McDermott,[4,5] Elizabeth R Plimack,[6] Philippe Barthélémy,[7,8] Camillo Porta ,[9] Thomas Powles,[10,11] Frede Donskov,[12] Saby George,[13] Christian K Kollmannsberger,[14] Howard Gurney,[15,16] Marc-Oliver Grimm,[17] Yoshihiko Tomita,[18] Daniel Castellano,[19] Brian I Rini,[20] Toni K Choueiri,[21] Shruti Shally Saggi,[22] M Brent McHenry,[23] Robert J Motzer[24]

And furthermore, as @ERPlimackMD points out in another tweet, impt to look at primary PD rates (seen in @lalaniMD's table) - nivo/ipi at 19%!!! CR rate used to be something we highlighted w nivo/ipi, but now comparable across studies (3/15)

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PFS HR (95%CI)	0.74 (0.62-0.88)		0.71 (0.60-0.84)		0.51 (0.41-0.64)		0.39 (0.32-0.49)	

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Okay now to the really tough stuff - comparing TKI/IO regimens. Something interesting I will add to @brian_rini @uromigos table above is the HR for PFS by INVESTIGATOR review. If the diff in HR for PFS by IND review caught your eye, this is even more striking (4/15)

First-line IO Combination Trials in mRCC

	CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
mOS, months HR (CI);	NR vs 38.4 **0.69** (0.59–0.81);	NR vs 35.7 **0.68** (0.55-0.85);	NR vs NR **0.60** (0.40–0.89);	NR vs NR **0.66** (0.49-0.88)
Landmark OS 12 mo Landmark OS 24 mo	**83%** vs. 78% **71%** vs. 61%	**90%** vs. 79% **74%** vs. 66%	**87%** vs. 78% (est) **74%** vs 60% (est)	**90%** vs 79% (est.) **79%** vs 70%
mPFS, months HR (CI)	**12.2** vs 12.3 0.89 (0.76–1.05)	**15.4** vs 11.1 0.71 (0.60–0.84)	**16.6** vs 8.3 0.51 (0.41–0.64)	**23.9** vs 9.2 0.39 (0.32-0.49)
ORR, %	**39** vs 32	**60** vs 40	**56** vs 27	**71** vs 36
CR, %	**11** vs 3	**9** vs 3	**8** vs 5	**16** vs 4
Med f/u, months	**55**	**30.6**	**18.1**	**27**
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 therapies for sunitinib arm, %	Overall (69%) IO (42%)	Overall (69%) IO (48%)	Overall (40%) IO (29%)	NR

1. Albiges et al. ESMO Open 2020
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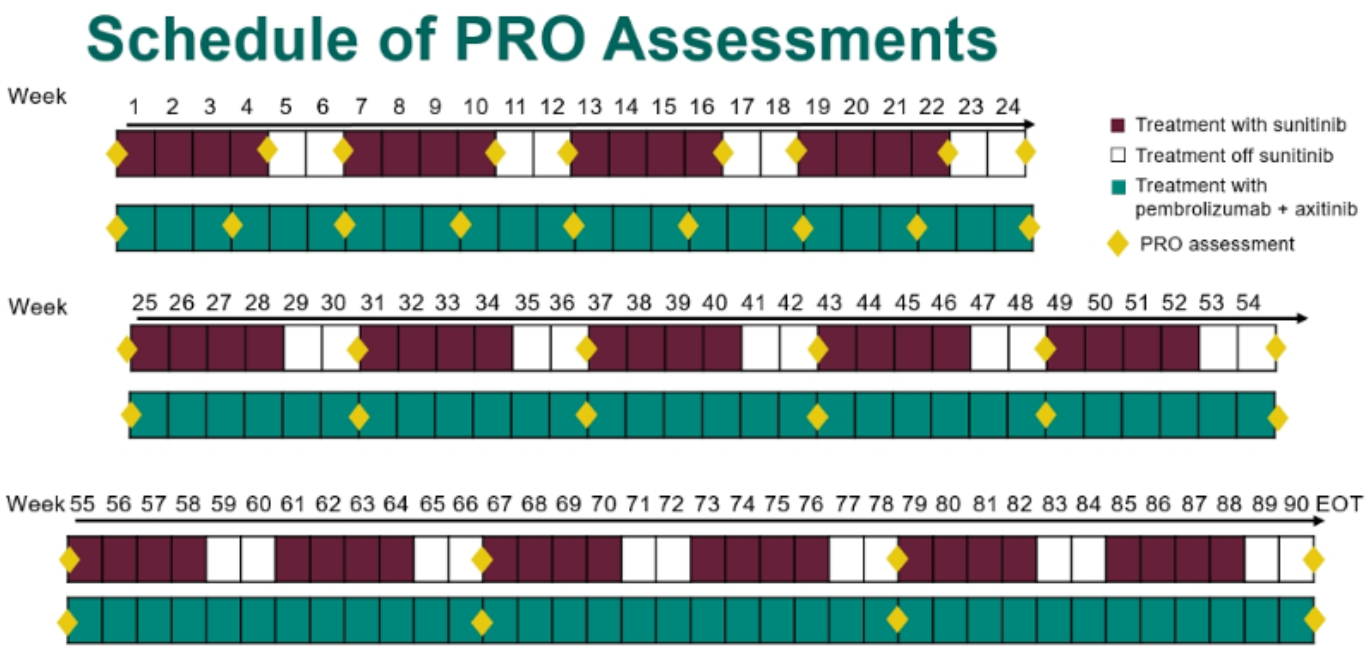
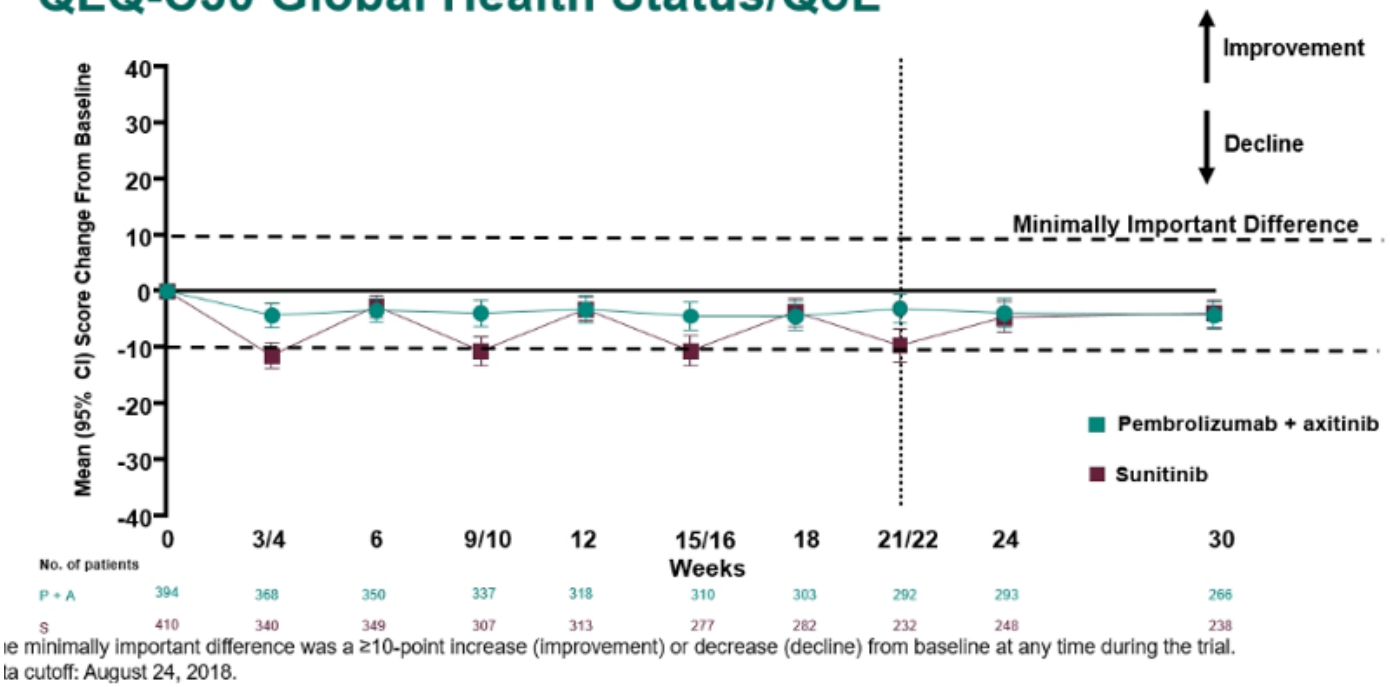
@brian_rini and @Uromigos (podcasts: https://anchor.fm/the-Uromigos)

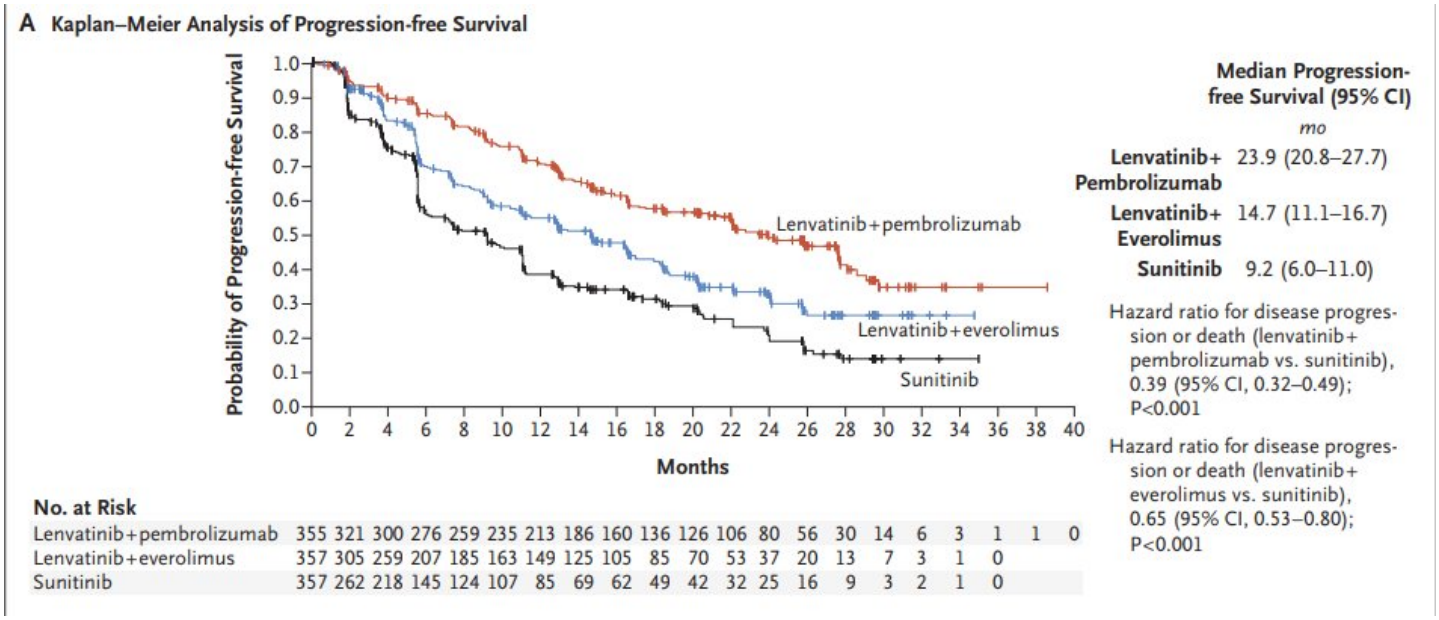
I think INV-assessed PFS is impt, but if you're a skeptic, forget that argument. Turn instead to #QOL with axi/pembro. Kudos to @brian_rini @tompowles1 @ERPlimackMD et al for advocating for QOL in KN-426. @crisbergerot et al have taughts us the importance of these metrics. (5/15)



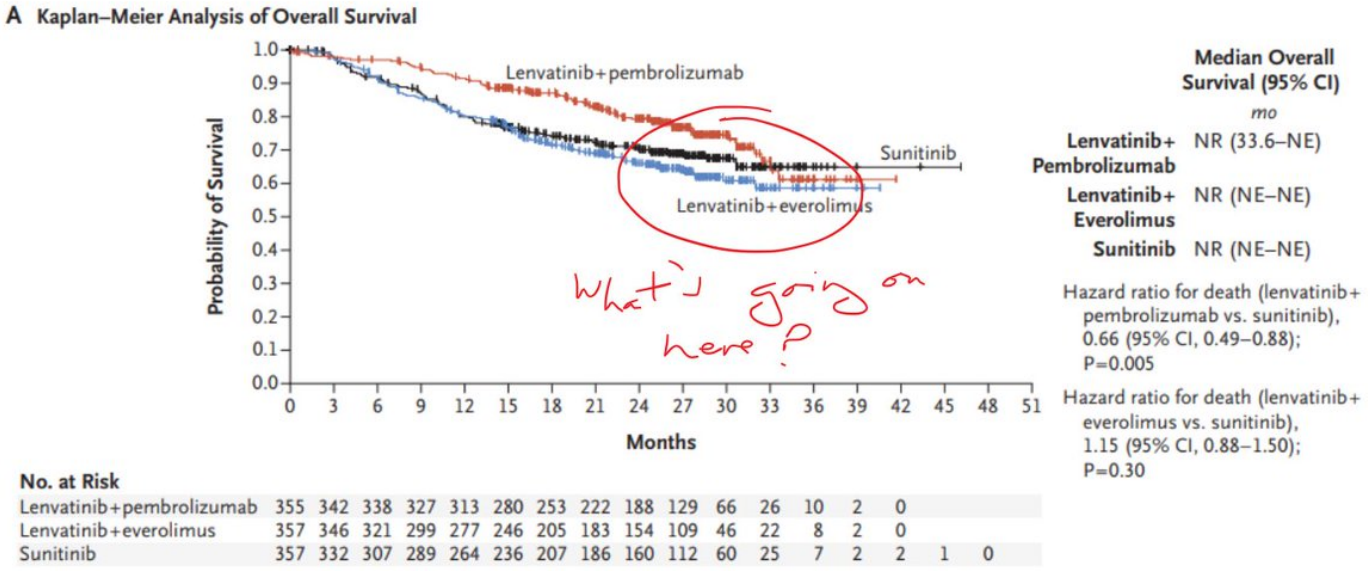
Unfortunately, we're not seeing any improvement in QOL w axi/pembro. This is a bit concerning - if balanced between arms, are we prolonging PFS at the expense of the patient's overall well-being? Inc tumor regression should be accompanied by some symptomatic improvement. (6/15)



Okay, now on to one of the headliners at @ASCO #GU21 this past weekend. The CLEAR study presented by @motzermd @DrChoueiri @DrTHut @tompowles1 @CPRT65 et al. Simultaneously published in @NEJM - congrats friends! (7/15)



Just one point on the curves, which I heard @tompowles1 bring up on a @Uromigos podcast w @DrChoueiri (of note, I also saw @manuelmaiamd bring this up during @motzermd's presentation in the @ASCO #GU21 pres). Why do the OS curves merge? Not so in #CheckMate9ER! (8/15)



Regardless, some may be swayed by the 16% CR rate with len/pembro. Now HERE is where we need to dive into baseline characteristics. Nearly 10% more fav risk in CLEAR, and also, more pts with prior neph. So, the odds of getting CR (or even PR) stacked against #CheckMate9ER (9/15)

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@brian_rini and @Uromigos (podcasts: https://anchor.fm/the-Uromigos)

I'll next make the point that LEN IS HARD TO TOLERATE. I'm glad @SoaresAndrey highlights the rate of discontinuation in #CLEAR, which appears much higher than in #CheckMate9ER. I've seen 7al versions of the data, but no matter how you slice it, d/c rate■■with len/pembro. (10/15)

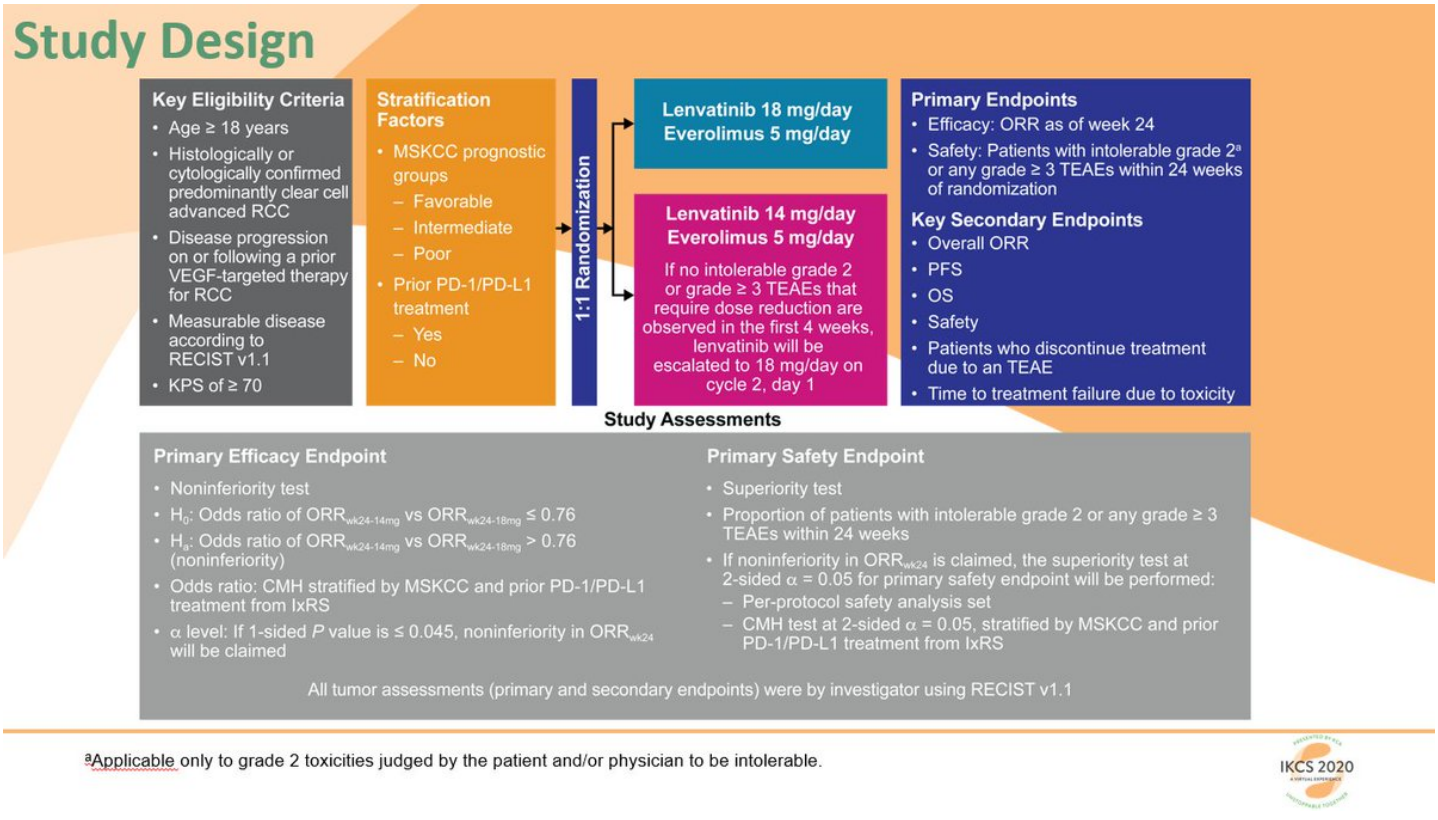
First Line RCC landscape

Primary endpoints

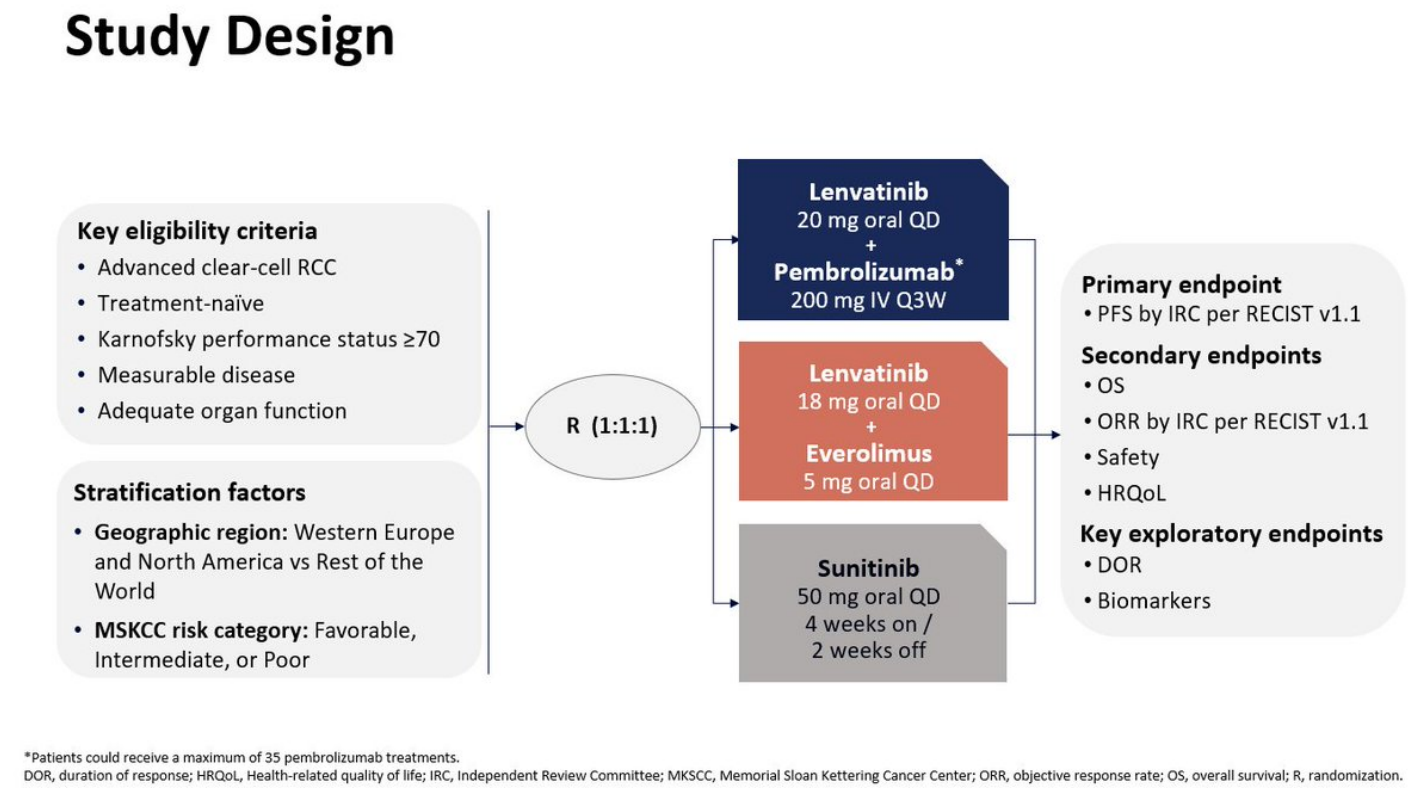
Study (primary population)	CM2141 (Int/Poor)	KN4262 (ITT)	JAVELIN3 (PD-L1+)	CM9ER4 (ITT)	KN5815 (ITT)
n	1096	861	560	651	1069
Follow-up	55 months	30.6 months	19.3 months	18.1 months	27 months
IMDC risk	61/17 23 (low risk)	31.9/55.1/13	19.3/66.7/12.2	22.6/57.6/19.7	31/59.2/9.3
Prior nephrectomy	82% x 80%	82.6% x 83.4%	86.3% x 86.9%	?	73.8% x 72.8%
ORR (%)	41.9% x 26.8%	60% x 40%	55.9% x 27.2%	55.7% x 27.1%	71% x 36.1%
CR (%)	10.4% x 1.4% (p<0.0001)	9% x 3%	5.6% x 2.4%	8% x 4.6%	16.1% x 4.2%
PD as best response	19.3% x 16.8%	11% x 17%	11.5% x 22.4%	5.6% x 13.7%	5.4% x 14%
mPFS (m)	11.2 x 8.3 (HR: 0.74; p<0.01)	15.4 x 11.1 (HR; 0.71; p<0.0001)	13.8 x 7.0 (HR: 0.62; p<0.0001)	16.6 x 8.3 (HR 0.51, p<0.0001)	23.9 x 9.2 (HR: 0.39, p<0.001)
mOS (m)	48.1 x 26.6 (HR: 0.65; p<0.0001)	NR x 35.7 (HR: 0.68; p=0.0003)	NR x 28.6 (HR: 0.83; p=0.13)	NR x NR (HR 0.6, P=0.0[illegible]1)	NR x NR (HR: 0.66; p=0.005)
TRAE G3-5	47.9% x 64.1%	62.9% x 58.1%	56.7% x 55.4%	61% x 51%	71.6% x 58.8%
High dose corticosteroids	~35%	~15%	11.1%	10%	[illegible]
Discontinuation	22.1%	8.2%	7.6%	3.1%	13.4%
QoL	Yes	No	?	Yes	[illegible]

1. Alb[illegible] Society for Medical Oncology 2020 Virtual Congress (ESMO 2020); Abstract 711P.; 2. Lancet Oncol. 2020, October 23; 3. Ann Oncol. 2020 Apr 25;S0923-7534([illegible]39308-X; 4. *Annals of Oncology*, Volume 31 Supplement 4, Sep[illegible]ber 2020, Abstract 6960; https://www.elsat.com/news/2020/news202073.html

What's my experience with len? I ran a RP2 study w @DrDanielHeng @hipsytips @docjavip et al. We tried to lower dose from 18 to 14 mg & preserve efficacy, but with the caveat of this being a small non-inferiority study, it didn't appear feasible. ■rates of d/c due to AEs! (11/15)

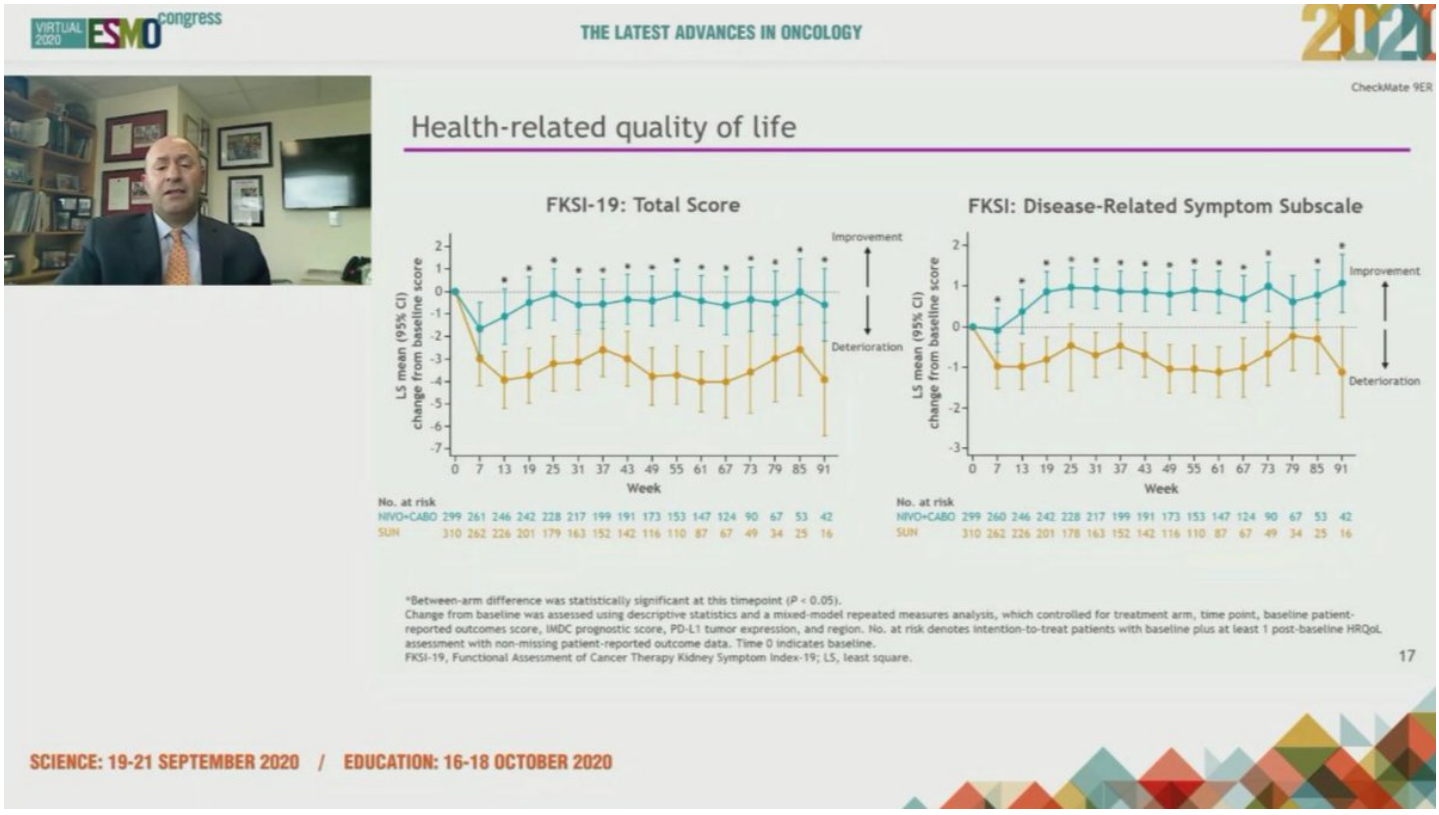


Remember, I was comparing 18 and 14 mg. The dose in #CLEAR even HIGHER at 20 mg! This is one of those settings where QOL data ESSENTIAL. Remember, our pts are thankfully doing better & will be on drug longer - we need to look out for their GLOBAL well-being! (12/15)



*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.

Now THIS is what we need to see. Improved QOL with cabo/nivo, as @DrChoueiri presented at #ESMO20. Remember, the dose of 40 mg is used in #CheckMate9ER - LOWER than the dose of 60 mg used in #METEOR, with cabo as 2L/3L tx. (13/15).



Confession: I was skeptical when @DrChoueiri @motzermd @tompowles1 @apolo_andrea & the brilliant team for #CheckMate9ER chose 40. But @neerajaiims & I have since reported data from #COSMIC021 (cabo/atezo across multiple settings). Efficacy at both doses seems quite good (14/15)

Study Design for Patients with ccRCC

Advanced or metastatic ccRCC
- No prior systemic therapy for RCC
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1

Expansion Cohorts

April 2018*	January 2019*
Cabozantinib 40 mg QD PO + Atezolizumab 1200 mg Q3W IV (N=30)	Cabozantinib 60 mg QD PO + Atezolizumab 1200 mg Q3W IV (N=30)

Tumor assessments per RECIST v1.1 by the investigator every 6 weeks for the first year and every 12 weeks thereafter; treatment until loss of clinical benefit or intolerable toxicity.

- 10 patients with previously untreated ccRCC were enrolled in the dose-escalation phase (4 at a dose level of 40 mg and 6 at a dose level of 60 mg)
- Data are presented for all 70 ccRCC patients with a data cutoff of July 21, 2020 and a median follow-up of 25.8 months (range, 20-33) for the 40 mg dose group and 15.3 months (range, 10-32) for the 60 mg dose group

Primary Endpoint: ORR by the investigator per RECIST v1.1
Secondary Endpoint: Safety
Exploratory endpoints include PFS and correlations of biomarkers with outcomes

VIRTUAL 2020 ESMO congress

*Date of the first patient enrolled.

SUMMARY: In 2021, we are blessed w gr8 data from mult 1L trials in #kidneycancer. I feel that cabo/nivo is the way to go; the goalpost is shifted beyond just PFS/RR/OS, we now need QOL! Thx to the amazing data summaries that facilitated this thread. Open to all comments. (15/15)