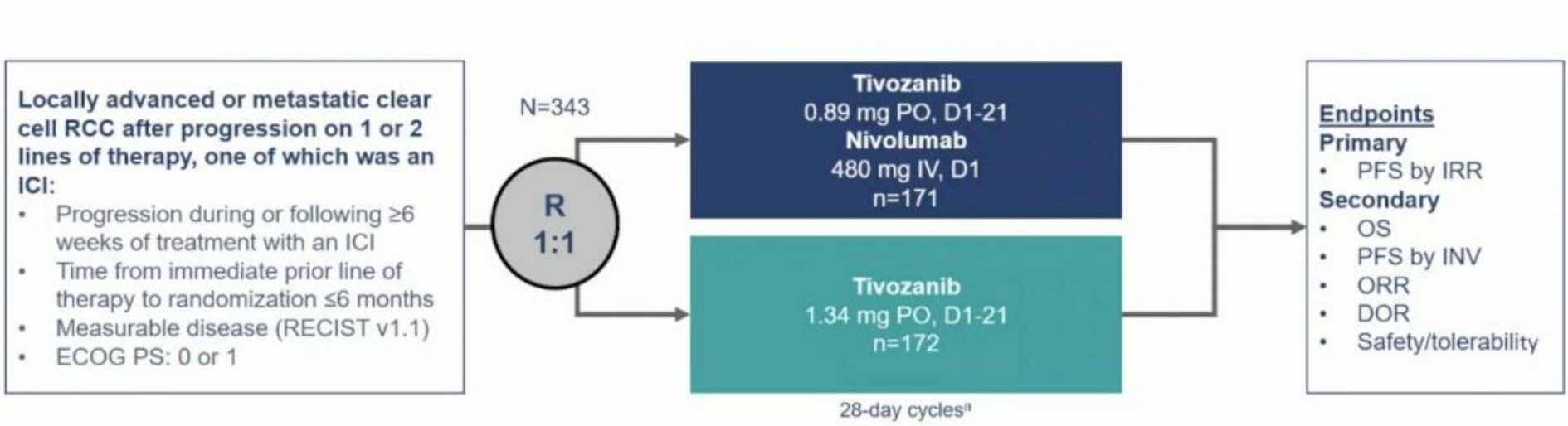
MLS IRVINE - ASCO/ESMO 2024 UPDATES - **RENAL CELL CARCINOMA**

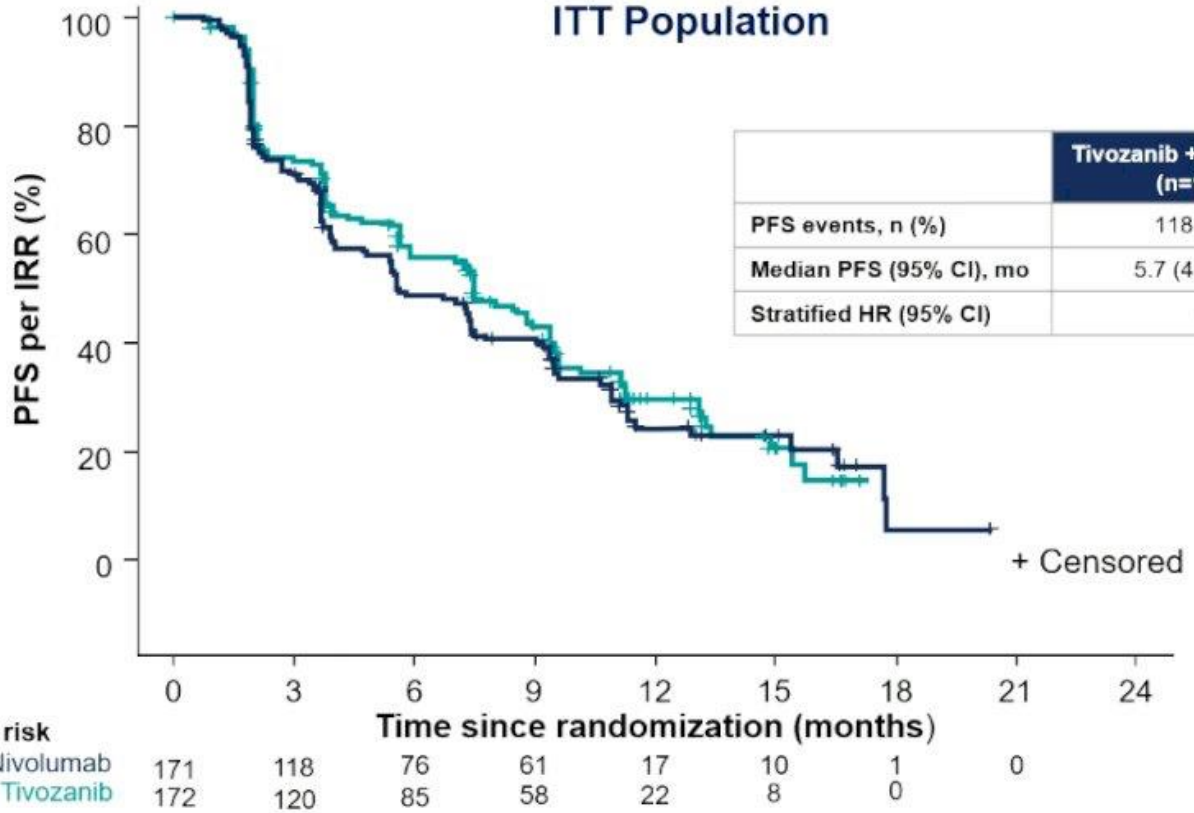
Nataliya Mar, MD
Clinical Associate Professor
Division of Hematology/Oncology
Department of Medicine
University of California Irvine
10/26/2024

Abstract #1

Choueiri, et al. *Tivozanib–nivolumab vs tivozanib monotherapy in patients with renal cell carcinoma (RCC) following 1 or 2 prior therapies including an immune checkpoint inhibitor (ICI): Results of the phase III TiNivo-2 study.*



Primary Analysis of Centrally Reviewed PFS (primary endpoint)

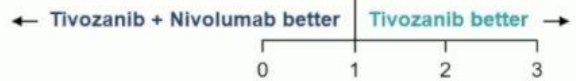


	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
PFS events, n (%)	118 (69)	112 (65)
Median PFS (95% CI), mo	5.7 (4.0-7.4)	7.4 (5.6-9.2)
Stratified HR (95% CI)	1.10 (0.84-1.43); p=0.49	

Median follow-up was 11.8 months in the tivozanib + nivolumab cohort and 12.5 months in the tivozanib monotherapy arm

Centrally Reviewed PFS by Subgroups

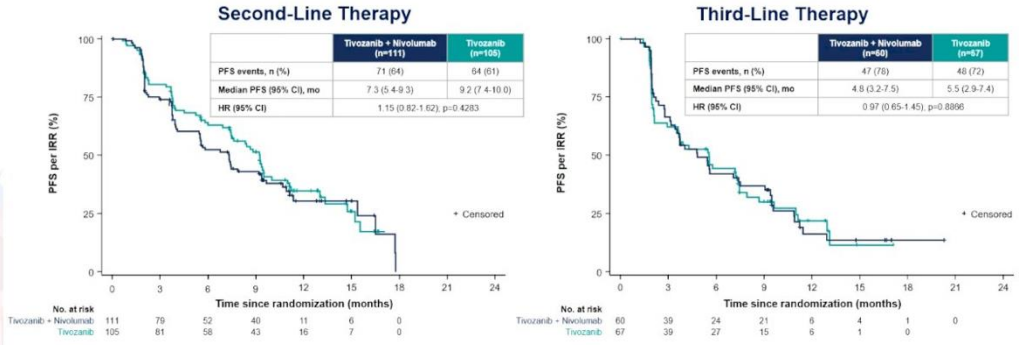
Category	Tivozanib + Nivolumab Event/N	Tivozanib + Nivolumab Median PFS (95% CI), months	Tivozanib Event/N	Tivozanib Median PFS (95% CI), months	PFS HR (95% CI)
Age					
<65 years	68/89	4.8 (3.7-7.3)	65/97	7.4 (5.5-9.2)	1.25 (0.89-1.76)
≥65 years	50/82	9.2 (5.5-9.6)	47/75	7.6 (5.2-10.0)	0.92 (0.61-1.37)
Sex					
Male	86/125	5.6 (3.9-7.5)	88/134	7.4 (5.5-9.2)	1.01 (0.75-1.36)
Female	32/46	6.7 (3.7-10.9)	24/38	7.4 (5.6-12.9)	1.27 (0.75-2.16)
ECOG PS					
0	52/76	7.3 (4.0-9.4)	53/85	8.8 (7.2-11.1)	1.15 (0.78-1.69)
1	66/94	5.5 (3.7-9.0)	59/87	6.0 (3.7-8.6)	0.95 (0.67-1.36)
IMDC risk category					
Favorable	18/30	9.3 (4.0-11.4)	15/31	11.2 (9.3-13.1)	1.37 (0.69-2.73)
Intermediate	78/114	5.7 (4.0-9.4)	75/115	7.4 (4.5-8.4)	0.99 (0.72-1.36)
Poor	22/27	3.7 (2.7-7.4)	22/26	5.7 (2.3-9.2)	1.35 (0.73-2.50)
VEGFR-TKI use in most recent line					
Yes	37/45	3.4 (2.2-4.8)	37/50	3.7 (1.9-7.2)	0.96 (0.61-1.52)
No	37/66	9.6 (7.5-11.2)	36/65	9.3 (7.4-14.7)	0.95 (0.60-1.51)
No. of previous VEGFR-TKIs (any prior line)					
0	29/53	9.6 (7.4-15.3)	28/53	9.4 (7.4-15.5)	1.03 (0.61-1.74)
1	69/96	5.4 (3.7-6.7)	70/101	7.4 (5.5-8.8)	1.04 (0.74-1.45)
2	20/22	3.1 (2.1-4.0)	14/18	3.8 (1.9-7.2)	1.33 (0.67-2.65)



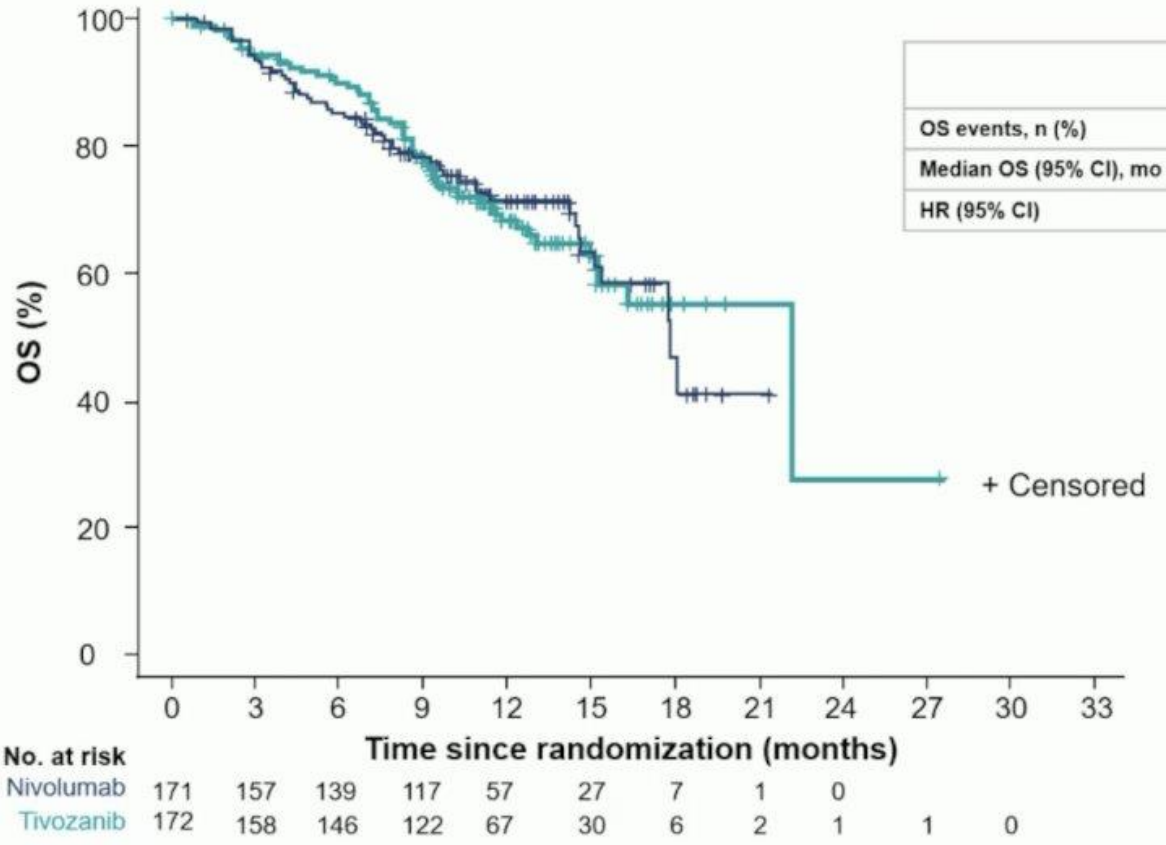
BARCELONA 2024 ESMO congress

ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ICI, immune checkpoint inhibitor; IMDC, International mRCC Database Consortium; IRR, independent radiology review; PFS, progression-free survival; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.

Centrally Reviewed PFS by Line of Therapy



Overall Survival



	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
OS events, n (%)	53 (31)	57 (33)
Median OS (95% CI), mo	17.7 (15.1-NR)	22.1 (15.2-NR)
HR (95% CI)	1.00 (0.68-1.46); p=0.9868	

Overall survival data are not mature.
At data cutoff, 32% of events had occurred.

Best Overall Response per Central Review

	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
ORR, n (%) [95% CI]	33 (19.3) [13.7-26.0]	34 (19.8) [14.1-26.5]
CR, n (%)	1 (0.6)	1 (0.6)
PR, n (%)	32 (18.7)	33 (19.2)
SD, n (%)	74 (43.3)	81 (47.1)
PD, n (%)	49 (28.7)	43 (25.0)
NE, n (%)	15 (8.8)	14 (8.1)
mDOR (95% CI), mo	15.77 (5.65-NR)	9.66 (3.71-NR)

Safety Summary

Adverse event	Tivozanib 0.89 mg + Nivolumab (n=168)	Tivozanib 1.34 mg (n=171)
Any-cause TEAE, n (%)	**163 (97)**	**167 (98)**
Related TEAE	137 (82)	144 (84)
Tivozanib	135 (80)	144 (84)
Nivolumab	119 (71)	0
Grade ≥3 AE, n (%)	**102 (61)**	**103 (60)**
Related	54 (32)	60 (35)
Serious AE, n (%)	**54 (32)**	**64 (37)**
Related	14 (8)	15 (9)
Death due to AE, n (%)	**7 (4)**	**5 (3)**
Related	0	1 (<1)
TEAE leading to discontinuation, n (%)	**27 (16)**	**33 (19)**
Due to tivozanib	19 (11)	33 (19)
Due to nivolumab	22 (13)	0
TEAE leading to dose interruption, n (%)	**82 (49)**	**93 (54)**
Due to tivozanib	79 (47)	93 (54)
Due to nivolumab	35 (21)	0
TEAE leading to dose reduction of tivozanib, n (%)	**18 (11)**	**38 (22)**
Median duration of treatment (range), months	**6.3 (0.0-20.7)**	**7.4 (0.1-17.9)**

Most Common All-Grade Adverse Events Regardless of Causality

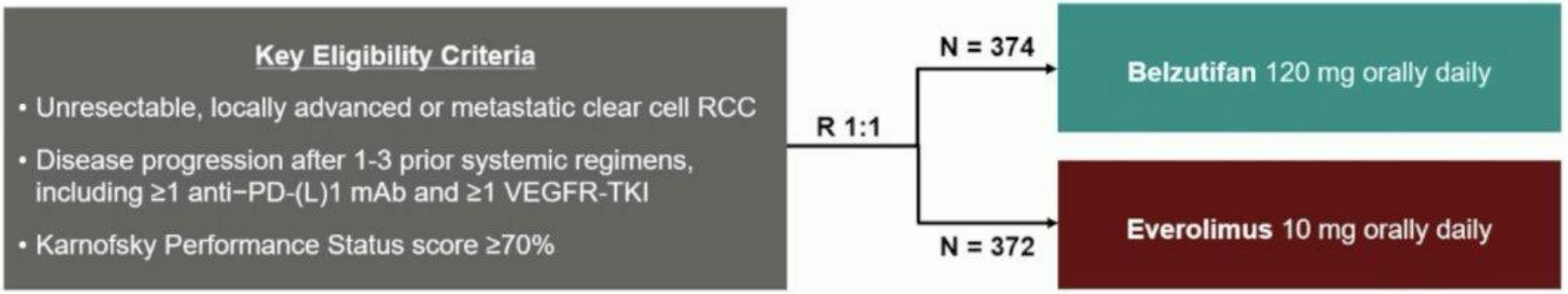
Adverse event, n (%)[a]	Tivozanib 0.89 mg + Nivolumab (n=168)	Tivozanib 1.34 mg (n=171)
Hypertension	62 (37)	69 (40)
Fatigue	49 (29)	68 (40)
Diarrhea	51 (30)	62 (36)
Nausea	26 (16)	47 (28)
Decreased appetite	37 (22)	46 (27)
Vomiting	20 (12)	36 (21)
Asthenia	39 (23)	35 (21)
Proteinuria	16 (10)	30 (18)
Constipation	17 (10)	29 (17)
Arthralgia	26 (16)	27 (16)
Cough	26 (16)	26 (15)
Hypothyroidism	15 (9)	26 (15)
Anemia	28 (17)	16 (9)
Pruritus	26 (16)	11 (6)

Takeaways:

- TiNivo-2 confirms and expands on data from the CONTACT-03 study, suggesting that IO re-challenge should NOT occur post failure of IO.
- Reduced Tivozanib dose in the combination arm may have impacted results of the study.
- Results support activity of Tivozanib monotherapy as early as 2nd line of therapy in RCC post IO failure.

Abstract #2

Rini BI, et al. *Final analysis of the phase III LITESPARK-005 study of belzutifan versus everolimus in participants (pts) with previously treated advanced clear cell renal cell carcinoma (ccRCC)*



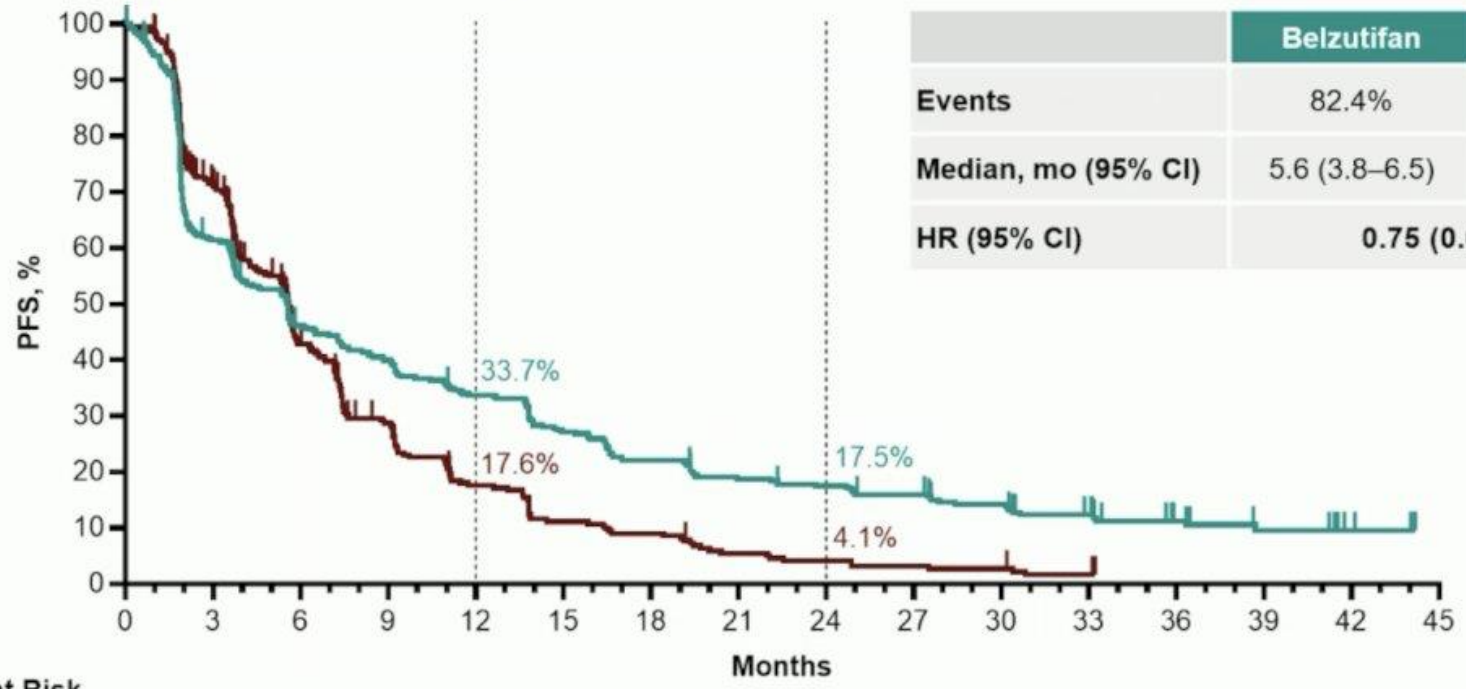
Stratification Factors
- IMDC prognostic score[a]: 0 vs 1-2 vs 3-6
- Prior VEGFR-targeted therapies: 1 vs 2-3

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

Primary Endpoint: PFS per RECIST 1.1 by BICR

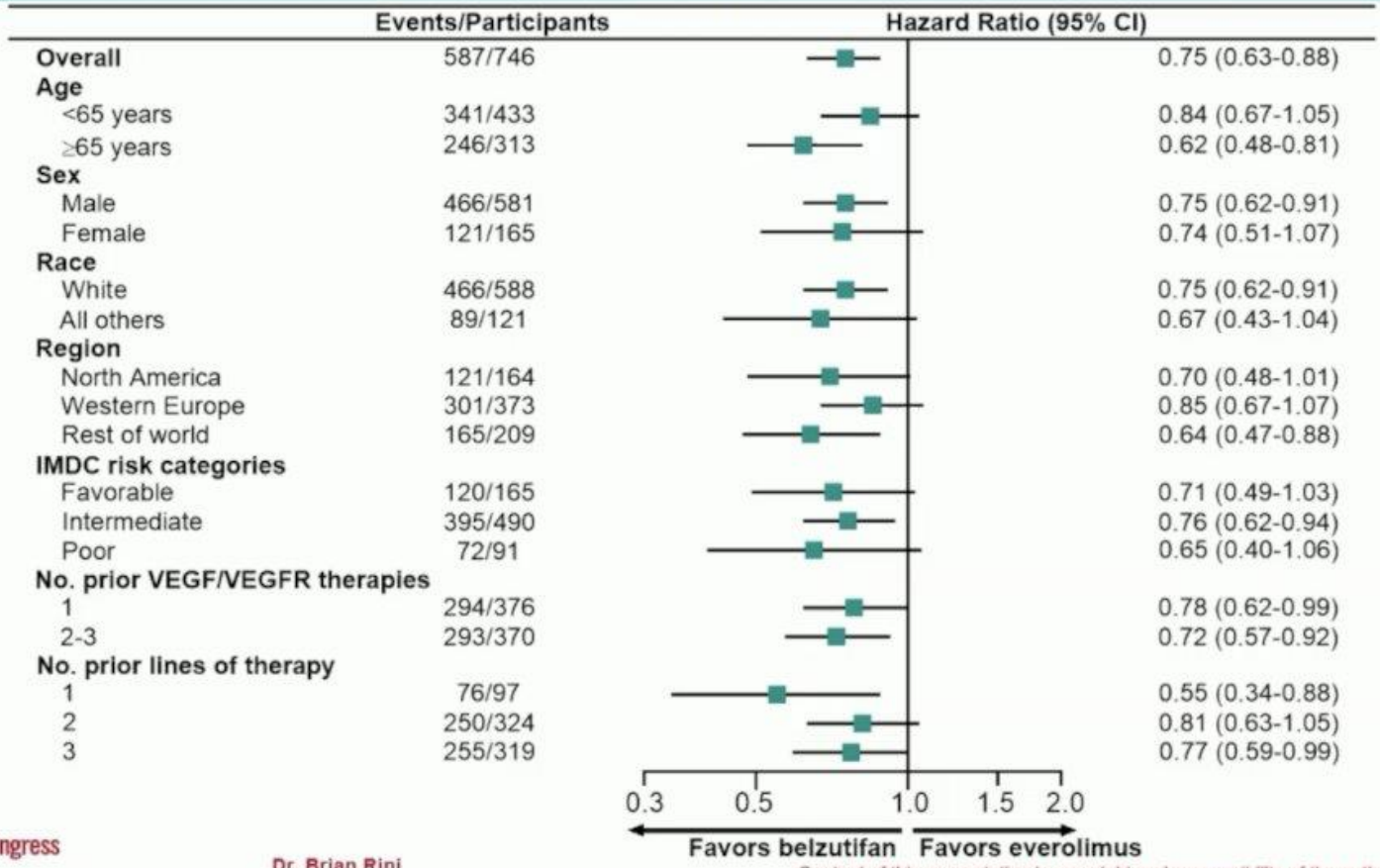


	Belzutifan	Everolimus
Events	82.4%	75.0%
Median, mo (95% CI)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.88)	

No. at Risk

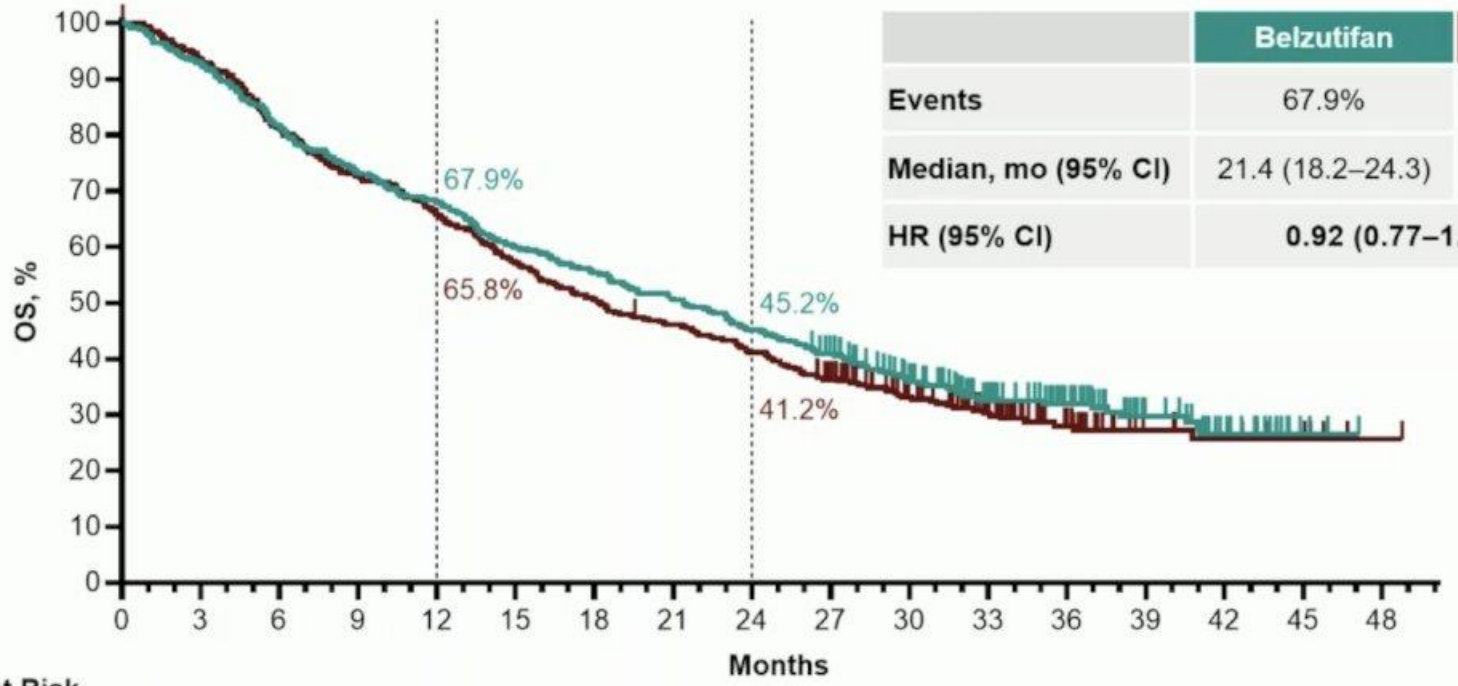
Belzutifan	374	218	156	135	113	91	74	61	56	50	39	27	16	10	5	0
Everolimus	372	226	113	70	41	26	21	12	9	7	6	3	0	0	0	0

PFS by BICR per RECIST 1.1 in Subgroups



Dr. Brian Rini

Primary Endpoint: OS



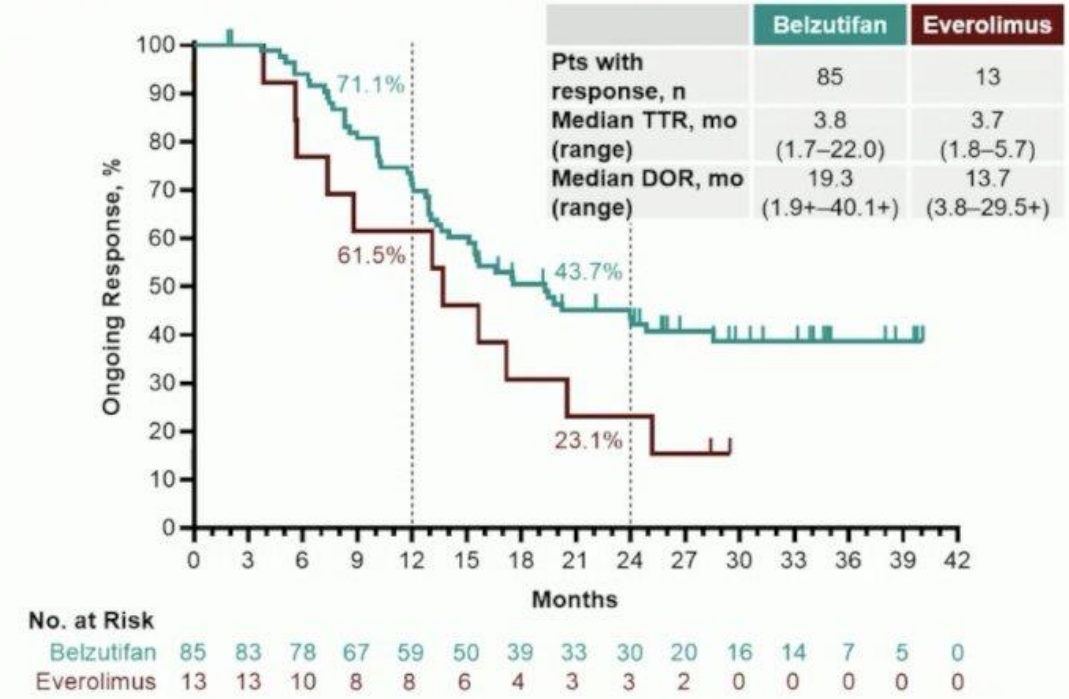
	Belzutifan	Everolimus
Events	67.9%	69.6%
Median, mo (95% CI)	21.4 (18.2–24.3)	18.2 (15.8–21.8)
HR (95% CI)	**0.92 (0.77–1.10); *P*=0.18**	

No. at Risk

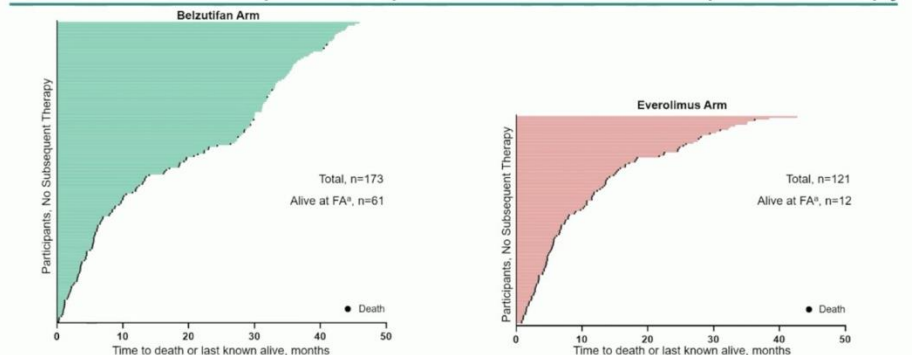
Belzutifan	374	347	305	274	254	224	207	189	169	148	111	75	54	31	18	4	0
Everolimus	372	347	301	270	244	212	188	170	152	128	92	64	38	20	12	5	1

ORR (Key Secondary) and DOR (Secondary Endpoint) by BICR per RECIST 1.1

	Belzutifan (N = 374)	Everolimus (N = 372)
ORR, % (95% CI)	**22.7% (18.6–27.3)**	**3.5% (1.9–5.9)**
Estimated difference in % (95% CI)	**19.2 (14.8–24.1)**	
Confirmed best objective response, %		
CR	3.5%	0
PR	19.3%	3.5%
SD	38.2%	65.9%
PD	34.0%	21.5%
Not evaluable[a]	1.3%	2.4%
No assessment[b]	3.7%	6.7%



Survival Follow-Up: Participants With No Subsequent Therapy



ADR	Incidence, n (%)	Time to onset, median (range), mo
Anemia	310 (83.3)	1.0 (0.03–27.4)
Hypoxia	53 (14.2)	1.0 (0.03–21.1)
Dizziness	50 (13.4)	2.3 (0.03–34.2)
Dyspnea	57 (15.3)	1.9 (0.03–25.8)
Fatigue	120 (32.3)	1.5 (0.03–29.9)
Nausea	69 (18.5)	1.4 (0.03–24.0)
Weight increased	22 (5.9)	3.3 (0.5–15.0)

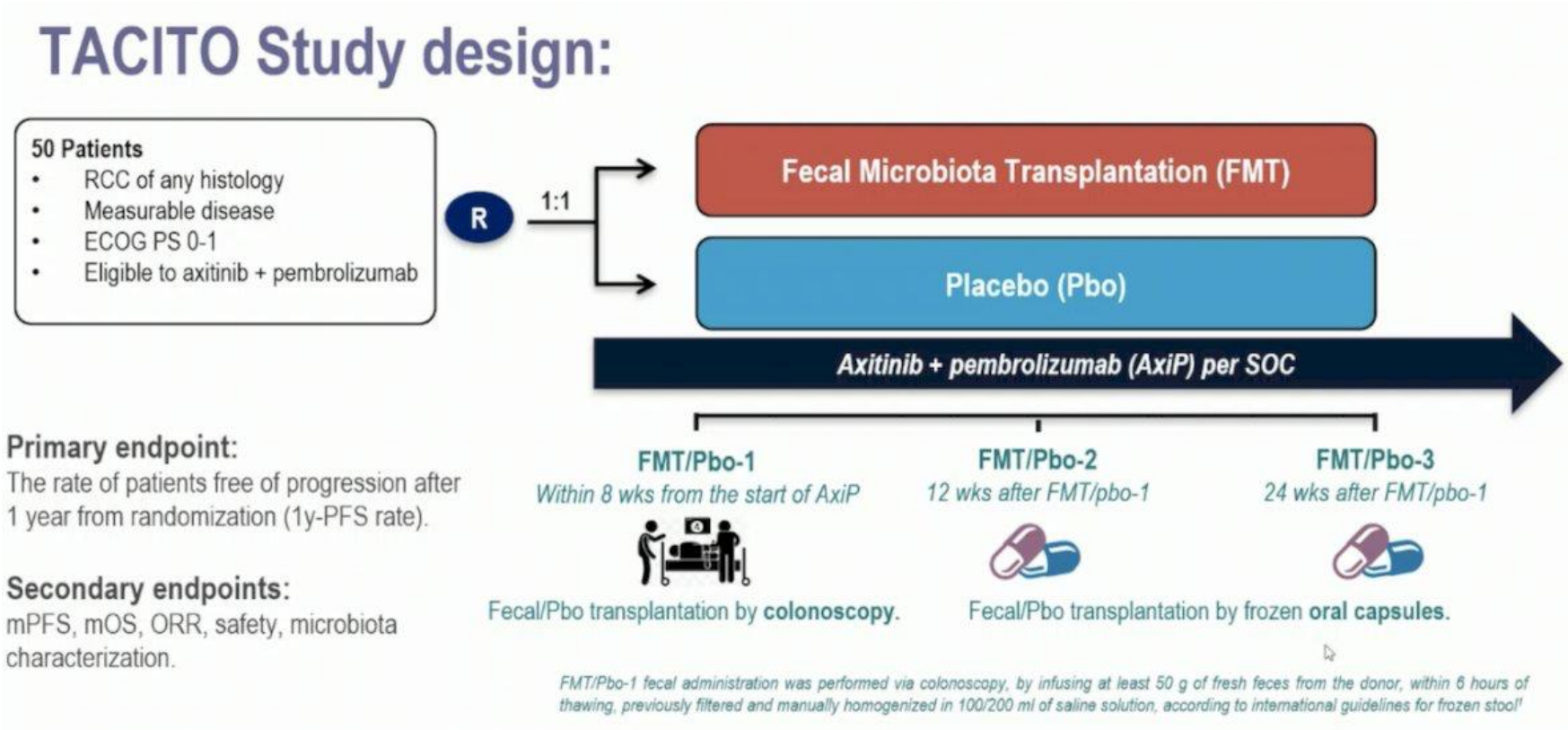
ADR	Incidence, n (%)	Duration, median (range), mo
Anemia	310 (83.3)	4.6 (0.1+–47.1+)
Hypoxia	53 (14.2)	0.5 (0.03–31.9+)
Dizziness	50 (13.4)	1.1 (0.03–35.2)
Dyspnea	57 (15.3)	3.3 (0.03–39.5+)
Fatigue	120 (32.3)	NR (0.1–43.9+)
Nausea	69 (18.5)	1.2 (0.03–38.6)
Weight increased	22 (5.9)	16.6 (0.6–40.0+)

Takeaways:

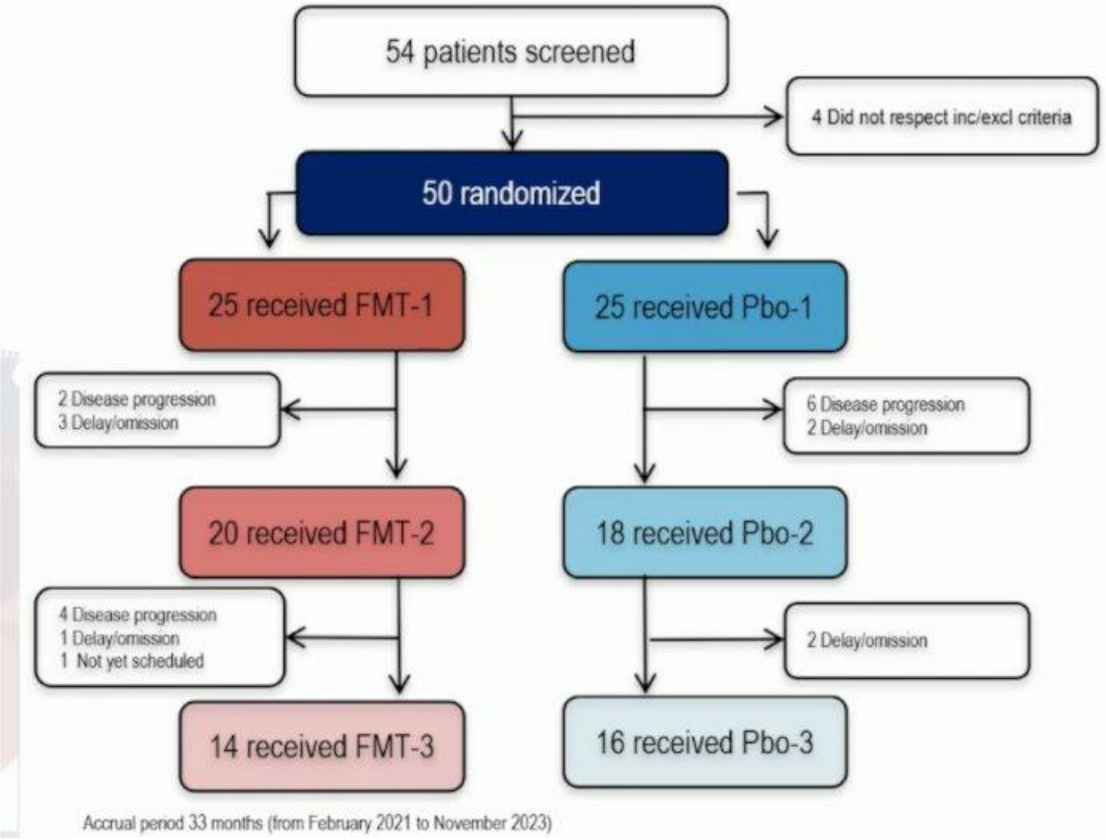
- At final analysis of LITESPARK-005, Belzutifan continues to show a PFS and ORR benefit versus Everolimus, with some responses lasting for >2 years.
- No OS benefit was observed.
- No new safety signals were observed. Median time to onset of most common TRAEs was <2 mos.
- This trial supports use of Belzutifan as a Tx option in advanced ccRCC, post-IO and post VEGF-TKI.

Abstract #3

Ciccarese C, et al. *Fecal microbiota transplantation (FMT) versus placebo in patients receiving pembrolizumab plus axitinib for metastatic renal cell carcinoma: Preliminary results of the randomized phase II TACITO trial.*



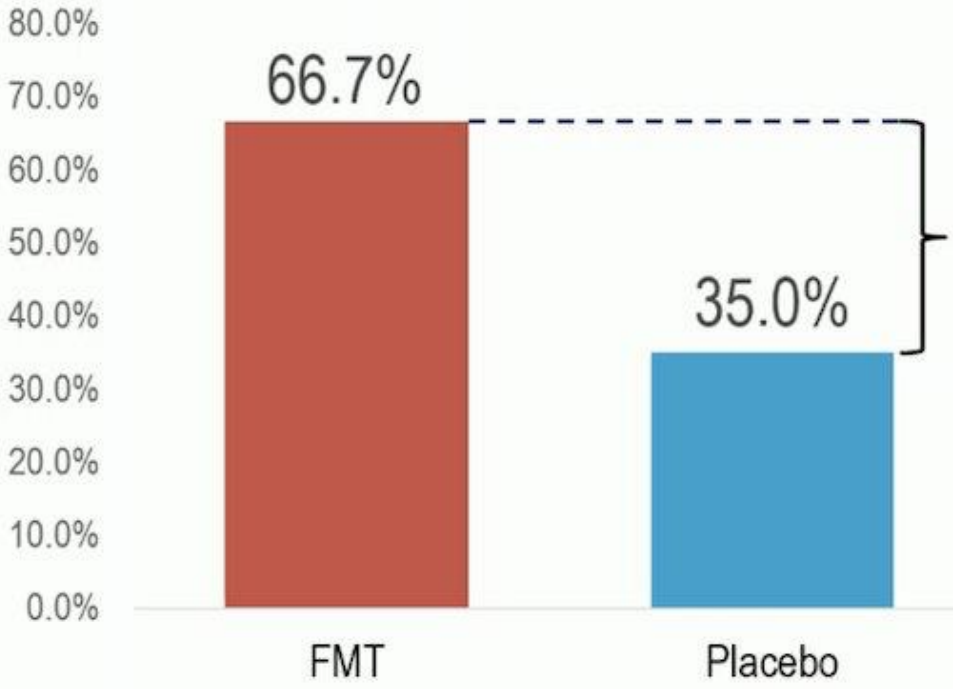
- Study donor - a 57 yo man with ccRCC s/p nephrectomy who developed >60 BL pulmonary mets and received Ipilimumab/Nivolumab, with CR.



Baseline characteristics	FMT N=25 (%)	Placebo N=25 (%)
Median age (years) (min-max)	61 (47 - 78)	61 (42 - 80)
Male sex	19 (76.0%)	19 (76.0%)
Nephrectomy	14 (56.0%)	16 (64.0%)
Tumor histology		
Clear cell	23 (92.0%)	21 (84%)
Papillary	1 (4%)	3 (12%)
Chromophobe	1 (4%)	1 (4%)
Sites of metastases		
Lung	19 (76.0%)	16 (64.0%)
Lymph node	9 (36.0%)	15 (60.0%)
Bone	7 (28.0%)	6 (24.0%)
Pancreas	6 (24.0%)	2 (8.0%)
Liver	3 (12.0%)	6 (24.0%)
IMDC prognostic class		
Favorable	7 (28.0%)	8 (32.0%)
Intermediate	14 (56.0%)	12 (48.0%)
Poor	4 (16.0%)	5 (20.0%)

Primary endpoint

Rate of patients free of progression after 1 year from randomization:



FMT increased the 1-y PFS rate of 31.7% compared to Pbo (p = 0.036)

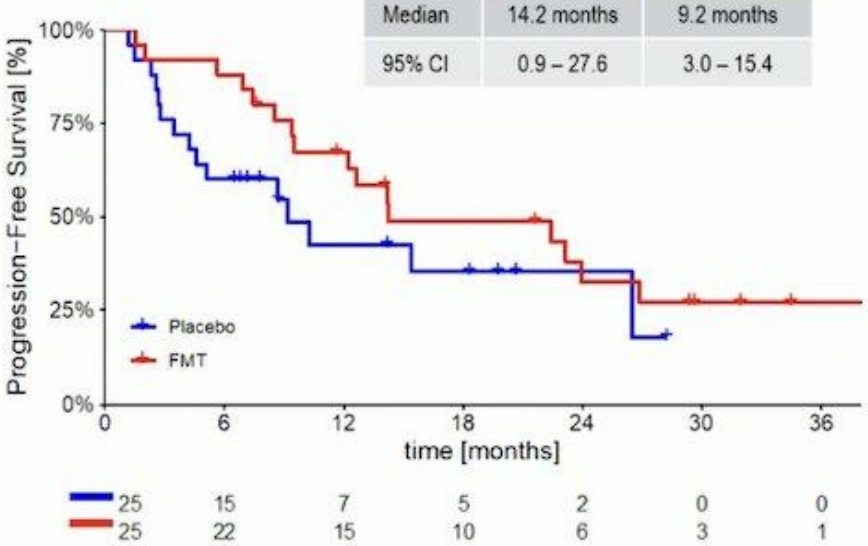
The primary endpoint was met.

44 patients had ≥12 months of follow-up: 24 (96%) FMT *vs.* 20 (80%) Pbo

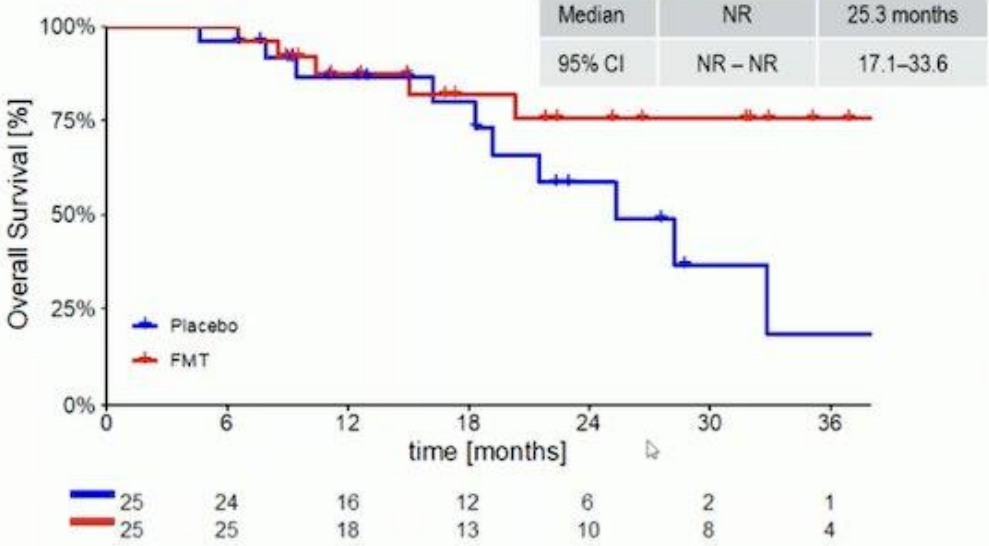
Secondary endpoints

PFS and OS in the overall population:

PFS	FMT N=25	Placebo N=25
Median	14.2 months	9.2 months
95% CI	0.9 – 27.6	3.0 – 15.4



OS	FMT N=25	Placebo N=25
Median	NR	25.3 months
95% CI	NR – NR	17.1–33.6



ORR in the overall population:

Tumor Response*	FMT N=25 (%)	Placebo N=25 (%)
Overall Response Rate	13 (52.0%)	7 (28.0%)
Complete response	0	0
Partial response	13 (52.0%)	7 (28.0%)
Stable disease	9 (38.0%)	11 (44.0%)
Progressive disease	2 (8.0%)	7 (28.0%)
Not evaluable	1 (4.0%)	0

Takeaways:

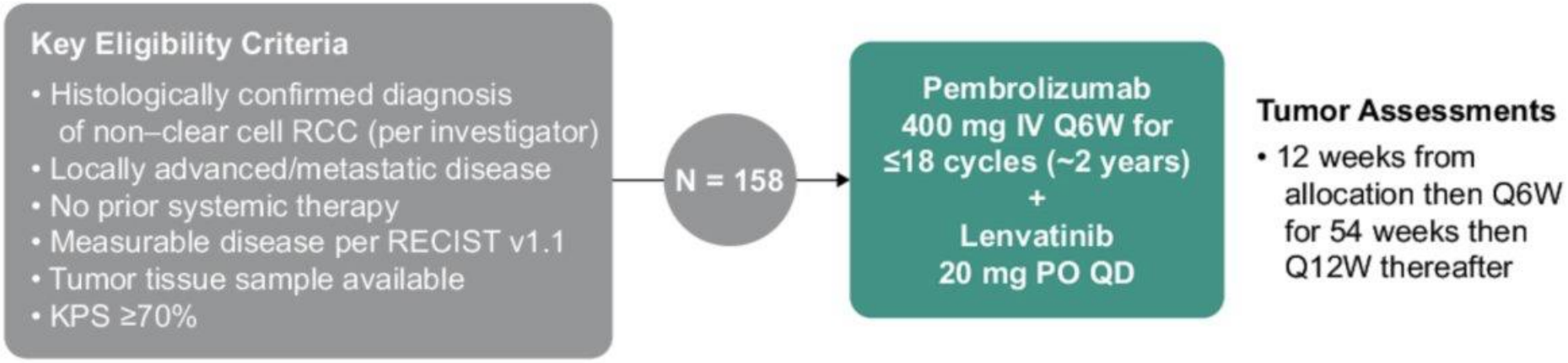
- TACITO highlights the active role of microbiome in RCC.
- FMT increased 1-year PFS compared to placebo in advanced RCC pts treated with Axi/Pembro.
- No severe AEs were noted with FMT.
- Longer F/U is needed for median PFS and OS.

Abstract #4

Voss MH. *First-line pembrolizumab plus lenvatinib for non–clear cell renal carcinomas (nccRCC): Extended follow-up of the phase 2 KEYNOTE-B61 study.*

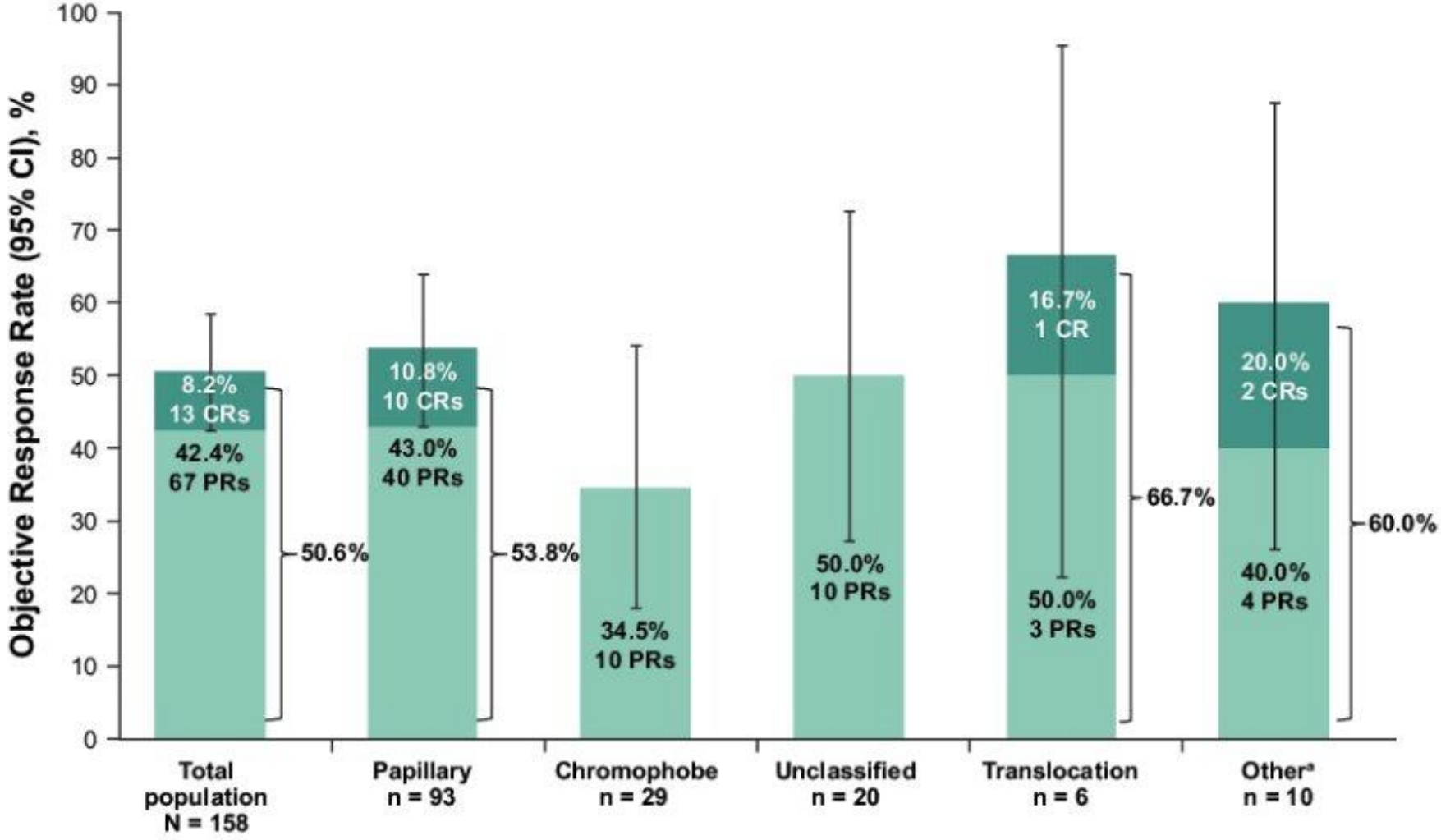
Lee C-H. *First-line lenvatinib + pembrolizumab treatment across non-clear cell renal cell carcinomas: Results of the phase 2 KEYNOTE-B61 study.*

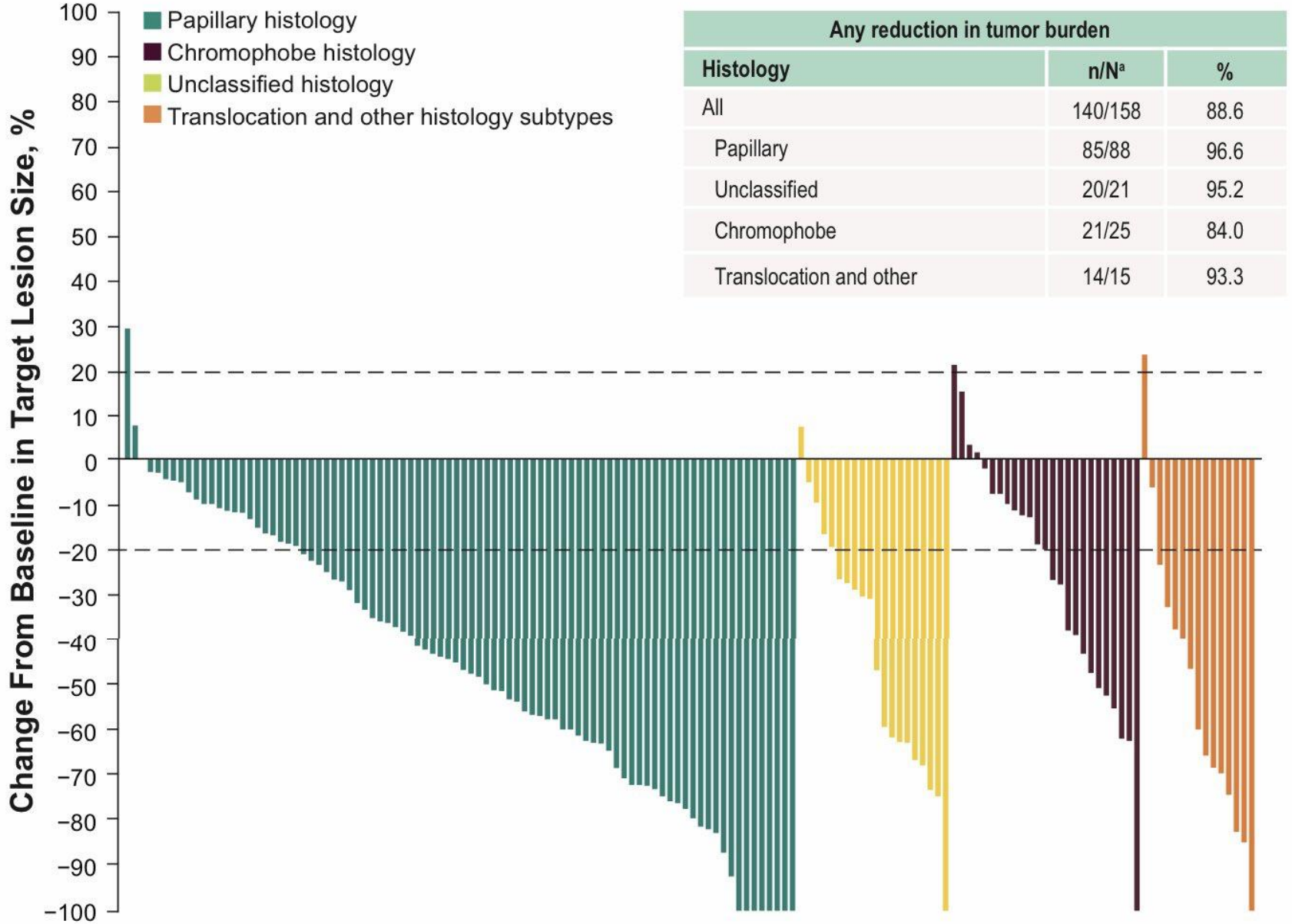
Figure 1. Study design



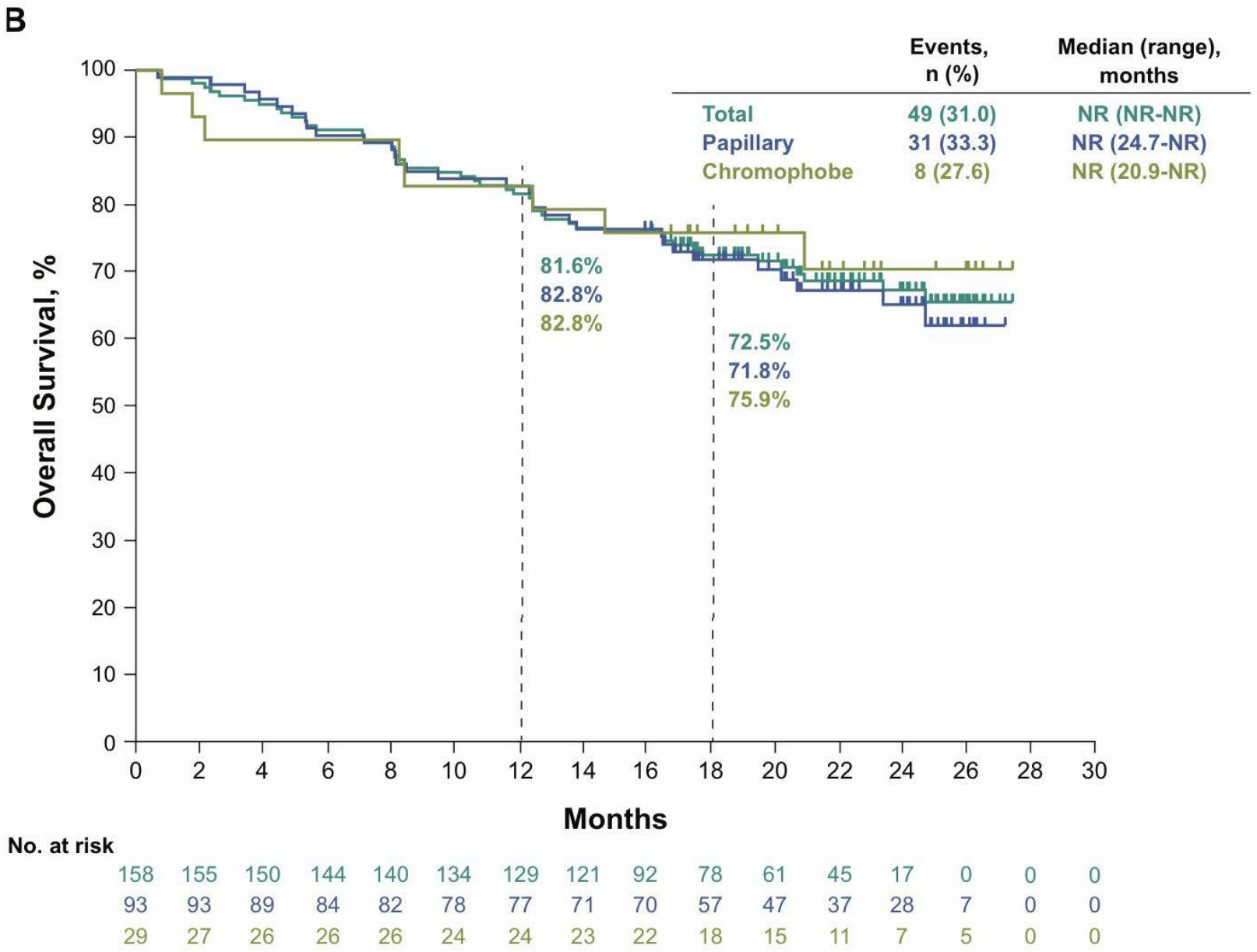
Primary endpoint - ORR per RECIST 1.1
Secondary endpoints - DCR, DoR, PFS, OS, safety

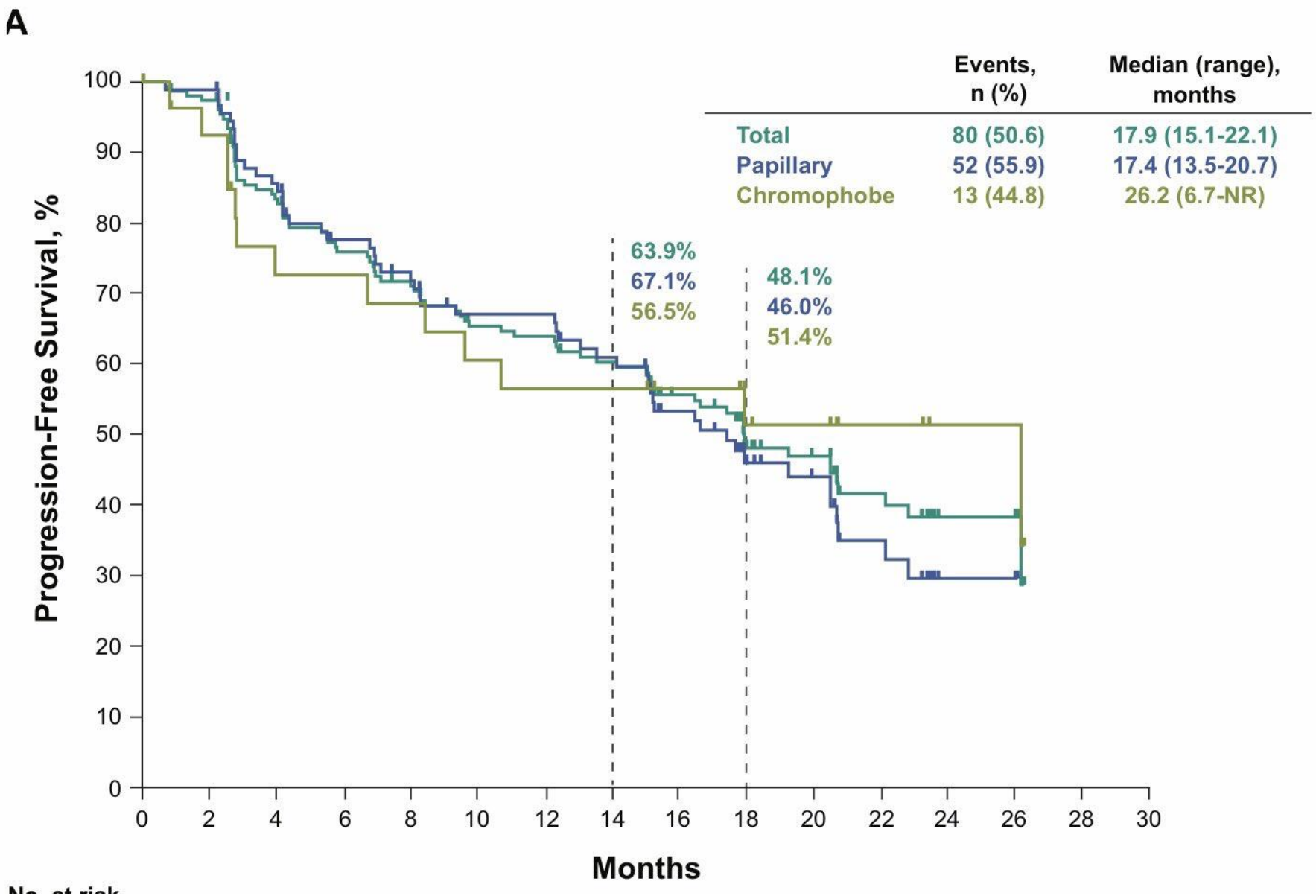
Figure 3. Confirmed ORR by histology per RECIST v1.1 by BICR





Any reduction in tumor burden		
Histology	**n/N[a]**	**%**
All	140/158	88.6
Papillary	85/88	96.6
Unclassified	20/21	95.2
Chromophobe	21/25	84.0
Translocation and other	14/15	93.3


B
Events, n (%)
Median (range), months
Total 49 (31.0) NR (NR-NR)
Papillary 31 (33.3) NR (24.7-NR)
Chromophobe 8 (27.6) NR (20.9-NR)
81.6%
82.8%
82.8%
72.5%
71.8%
75.9%
Overall Survival, %
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Months
No. at risk
158 155 150 144 140 134 129 121 92 78 61 45 17 0 0 0
93 93 89 84 82 78 77 71 70 57 47 37 28 7 0 0
29 27 26 26 26 24 24 23 22 18 15 11 7 5 0 0


A
Events, n (%)
Median (range), months
Total 80 (50.6) 17.9 (15.1-22.1)
Papillary 52 (55.9) 17.4 (13.5-20.7)
Chromophobe 13 (44.8) 26.2 (6.7-NR)
63.9%
67.1%
56.5%
48.1%
46.0%
51.4%
Progression-Free Survival, %
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Months

Event, %	Grade 1–2	Grade 3	Grade 4
Any	**43**	**46**	**5**
Hypertension	34	23	0
Diarrhea	41	3	0
Hypothyroidism	36	1	0
PPE	27	2	0
Dysphonia	28	0	0
Proteinuria	23	4	0
Fatigue	25	1	0
Decreased appetite	23	1	0
Nausea	23	1	0
Asthenia	18	3	0
Weight decreased	15	3	0
Stomatitis	14	4	0
Arthralgia	16	0	0
Mucosal inflammation	15	0	0

Tx D/C due to TRAEs occurred in:

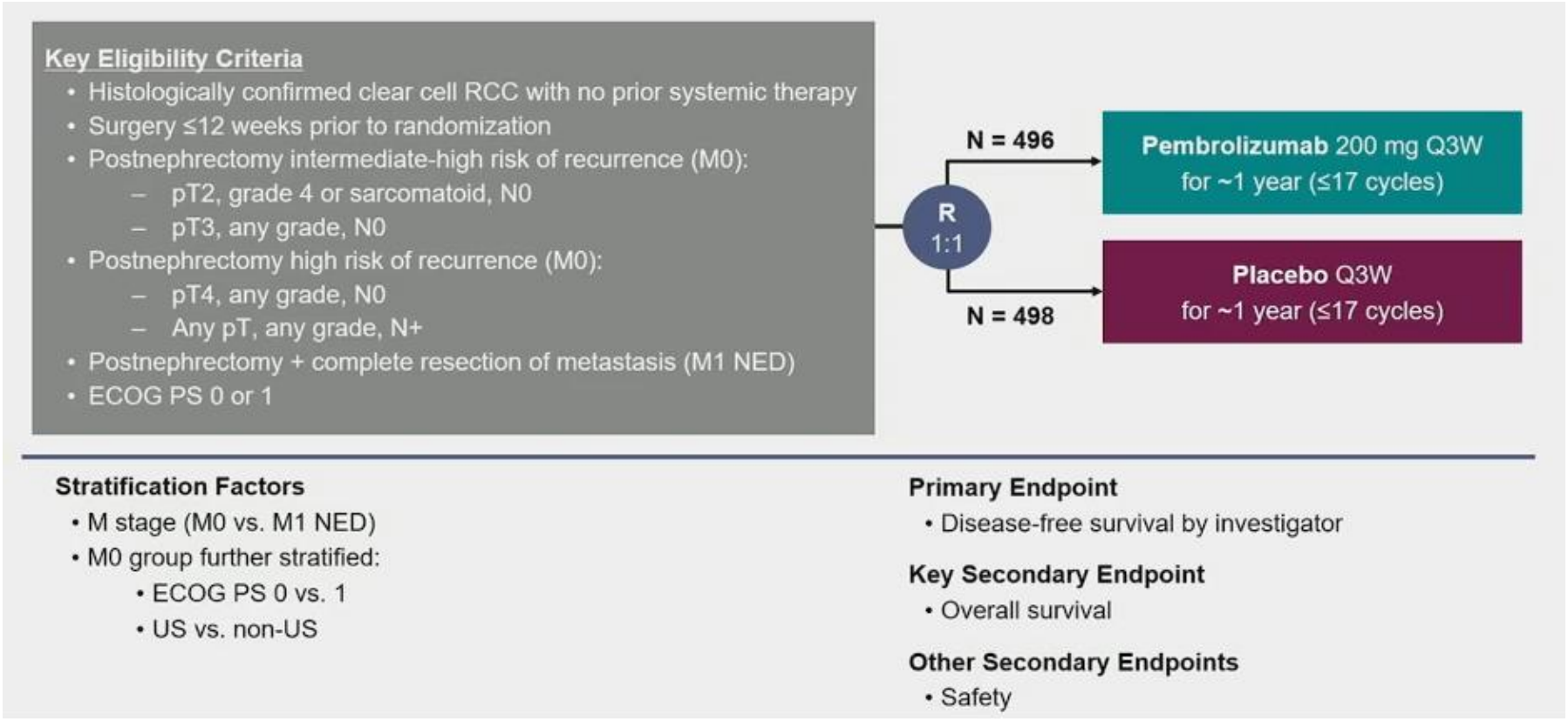
- **15% Pembro alone**
- **13% Lenvatinib alone**
- **4% both**

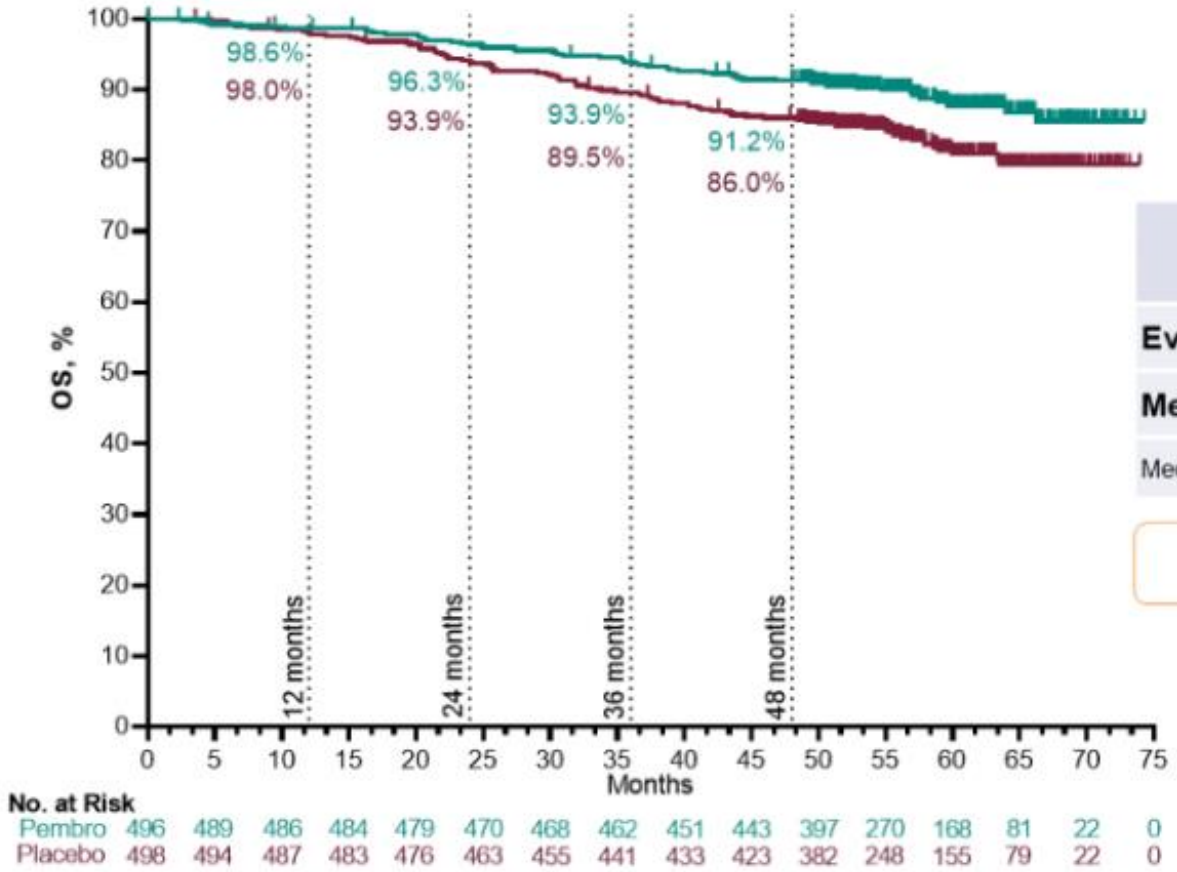
Takeaways:

- KeyNote B61 highlights activity of Pembro/Len in nccRCC across multiple histologies.
- This study supports use of this combination in the 1st line advanced nccRCC space.
- Pembro/Len has a tolerable safety profile.

Abstract #5

Choueiri TK, et al. *Overall survival results from the phase 3 KEYNOTE-564 study of adjuvant pembrolizumab versus placebo for the treatment of clear cell renal cell carcinoma (ccRCC).*





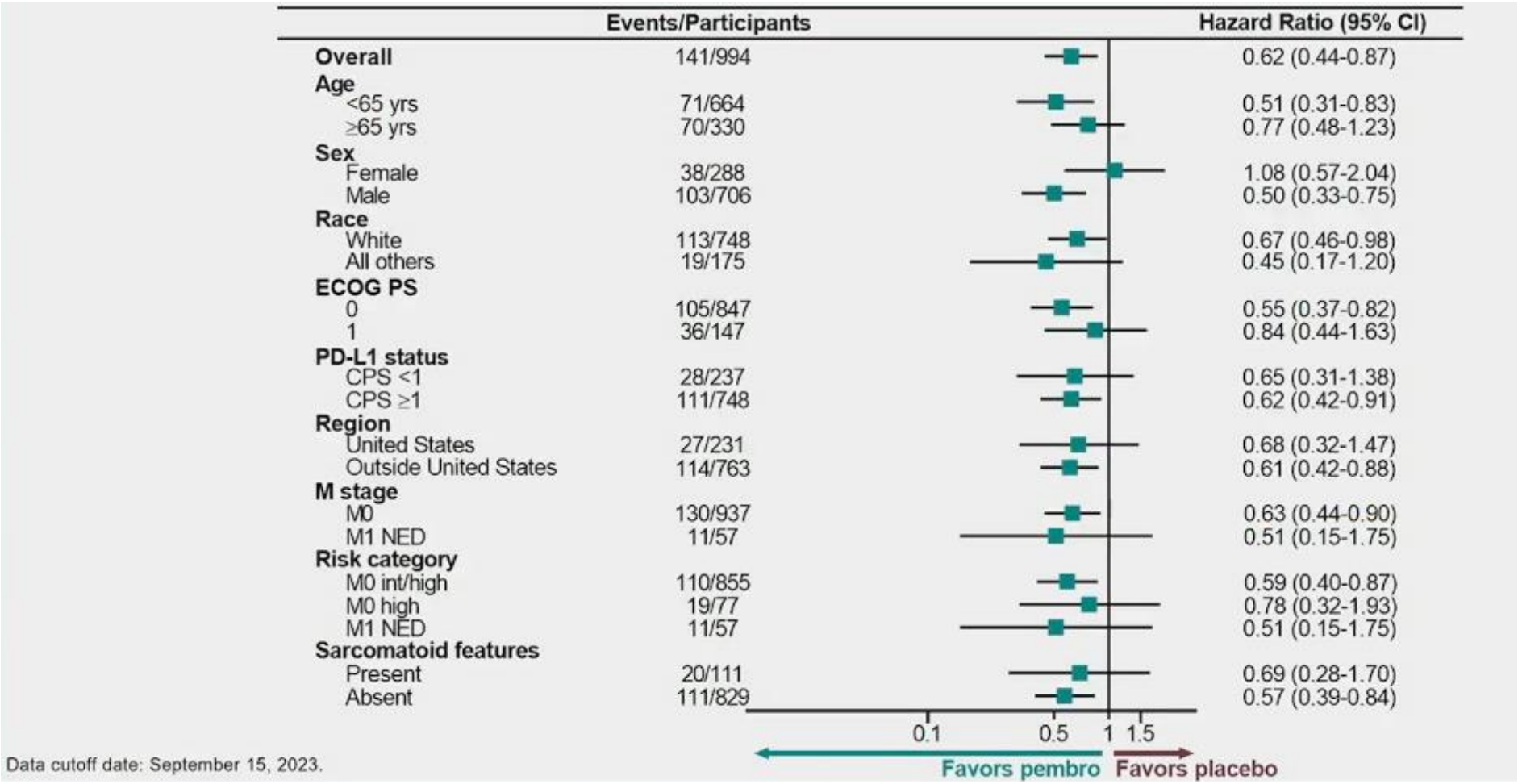
	Pembro (N = 496)	Placebo (N = 498)
Events, n	55	86
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)

Median follow-up was 57.2 months (range, 47.9–74.5)

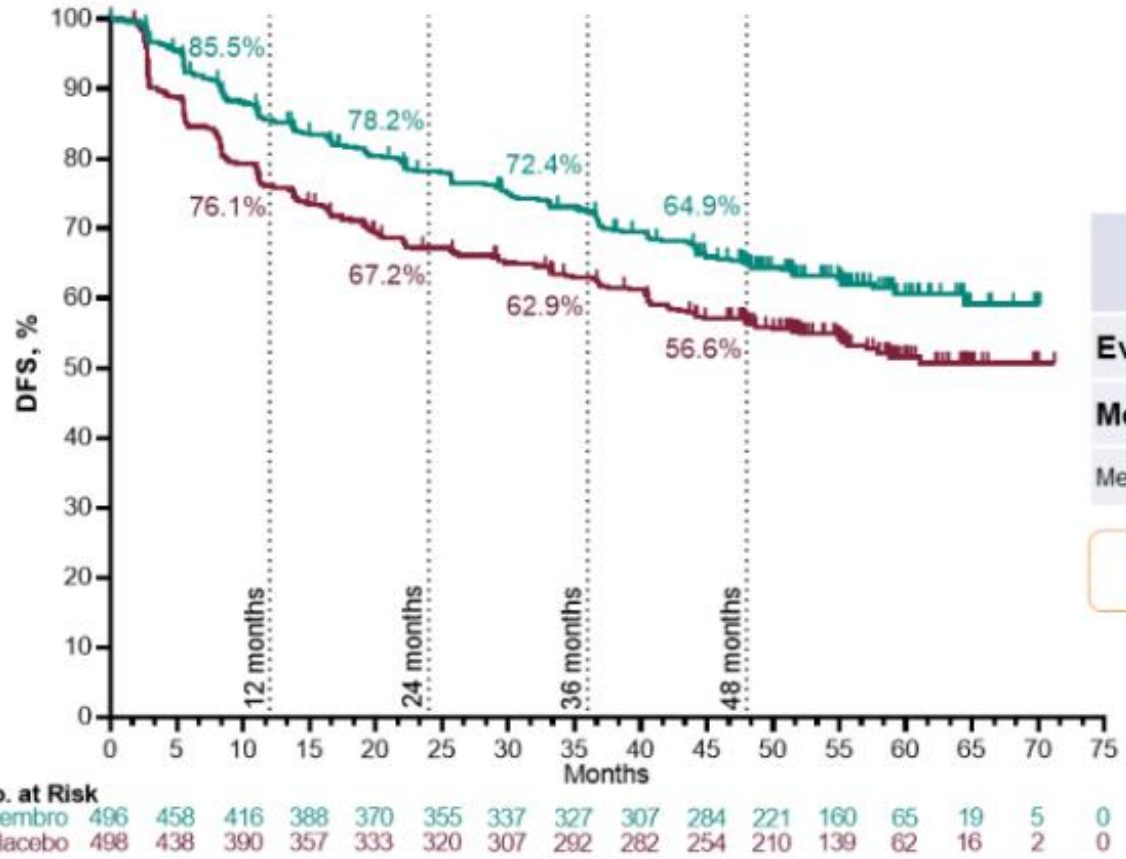
HR 0.62 (95% CI 0.44–0.87); *P* =.002*

* **denotes statistical significance**. P-value boundary for OS at IA3 was 0.0072 (1-sided) per Lan-DeMets O'Brien-Fleming spending approximation α-spending function. As this key secondary endpoint was formally met, any future OS analyses will be descriptive only.

Data cutoff date: September 15, 2023.



Data cutoff date: September 15, 2023.



	Pembro (N = 496)	Placebo (N = 498)
Events, n	174	224
Median, mo (95% CI)	NR (NR–NR)	NR (54.9–NR)

Median follow-up was 57.2 months (range, 47.9–74.5)

HR 0.72 (95% CI 0.59–0.87)

Primary DFS endpoint was met at IA1 and was not formally statistically tested thereafter.

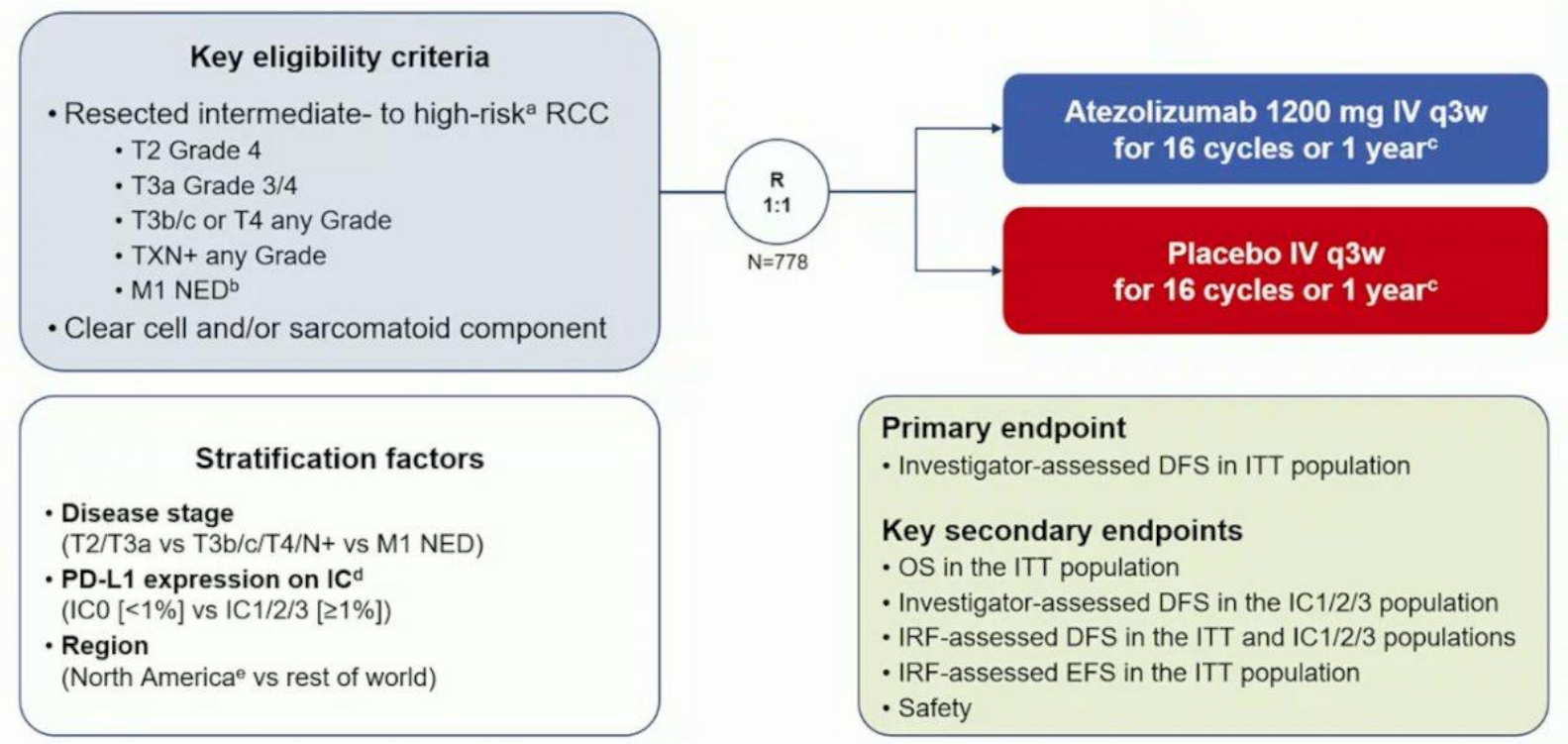
	Prior Analysis (30.1 mo follow-up)		IA3 (57.2 mo follow-up)	
	Pembrolizumab (N = 488)	Placebo (N = 496)	Pembrolizumab (N = 488)	Placebo (N = 496)
Duration of therapy, median (range), months	11.1 (0.03–14.3)	11.1 (0.03–15.4)	11.1 (0.03–14.3)	11.1 (0.03–15.4)
Any-cause AEs[a]	470 (96.3%)	453 (91.3%)	470 (96.3%)	453 (91.3%)
Grade 3 to 5	157 (32.2%)	88 (17.7%)	156 (32.0%)	88 (17.7%)
Led to treatment discontinuation	103 (21.1%)	11 (2.2%)	103 (21.1%)	11 (2.2%)
Led to death	2 (0.4%)	1 (0.2%)	2 (0.4%)	1 (0.2%)
Serious AEs[a]	101 (20.7%)	57 (11.5%)	101 (20.7%)	57 (11.5%)
Led to treatment discontinuation	49 (10.0%)	5 (1.0%)	49 (10.0%)	5 (1.0%)
Treatment-related AEs[a]	386 (79.1%)	265 (53.4%)	386 (79.1%)	263 (53.0%)
Grade 3 to 4	91 (18.6%)	6 (1.2%)	91 (18.6%)	6 (1.2%)
Led to treatment discontinuation	89 (18.2%)	4 (0.8%)	89 (18.2%)	4 (0.8%)
Led to death	0	0	0	0
Immune-mediated AEs and infusion reactions[b]	174 (35.7%)	34 (6.9%)	178 (36.5%)	36 (7.3%)
Grade 3 to 4	45 (9.2%)	3 (0.6%)	46 (9.4%)	3 (0.6%)
Led to death	0	0	0	0
Required high-dose (≥40 mg/day) systemic corticosteroids	37 (7.6%)	3 (0.6%)	37 (7.6%)	3 (0.6%)

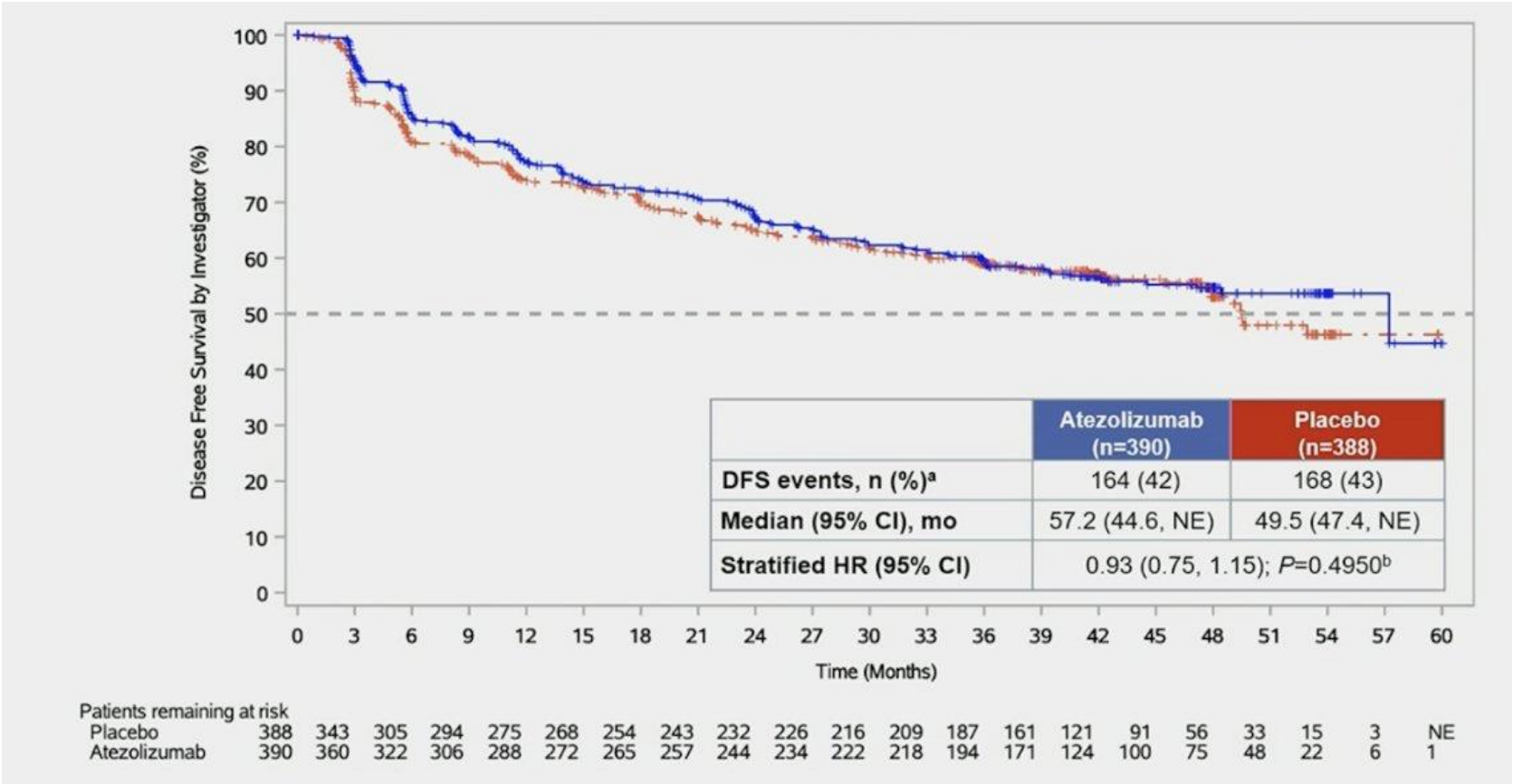
Takeaways:

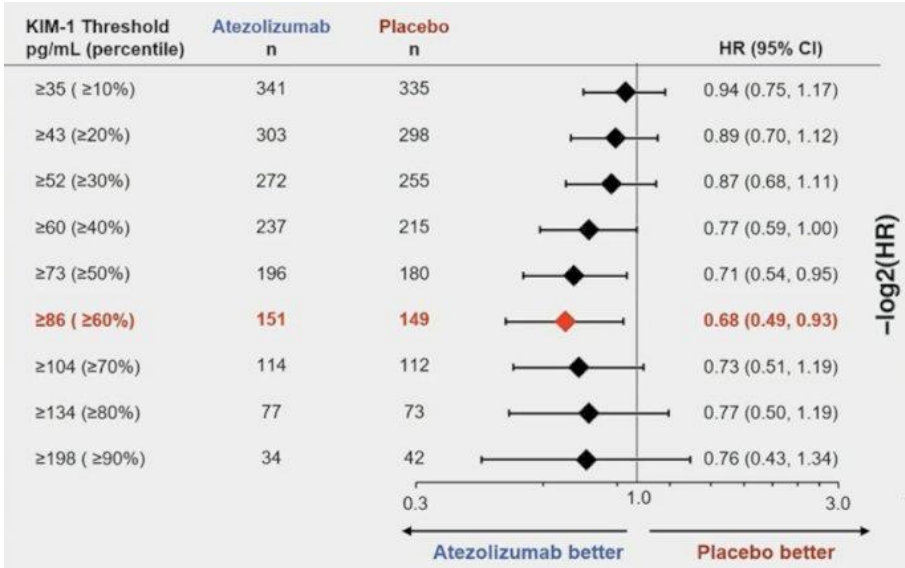
- Adjuvant Pembrolizumab significantly prolonged OS vs. placebo in pts with ccRCC at increased risk of recurrence post curative-intent surgery.
- Continued DFS benefit favoring Pembrolizumab was observed with longer F/U.
- No new safety signals were observed with longer F/U.
- This is the only study in adjuvant ccRCC space with an OS benefit.

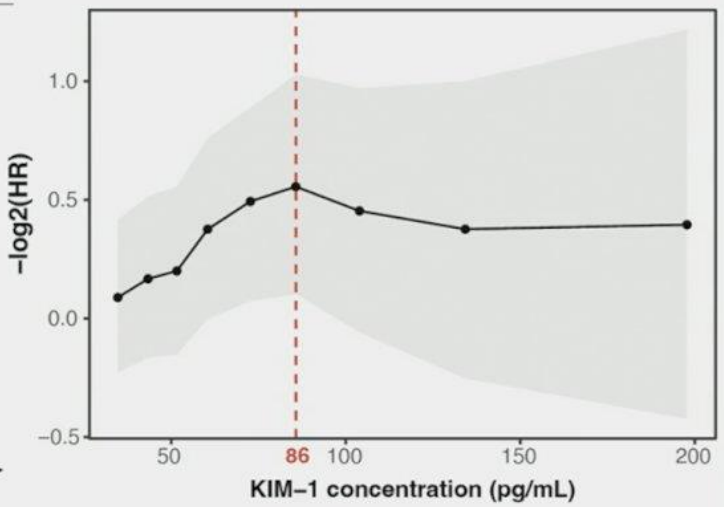
Abstract #6

Albiges L, et al. *Circulating kidney injury molecule-1 (KIM-1) biomarker analysis in IMmotion010: A randomized phase 3 study of adjuvant (adj) atezolizumab (atezo) vs placebo (pbo) in patients (pts) with renal cell carcinoma (RCC) at increased risk of recurrence after resection.*



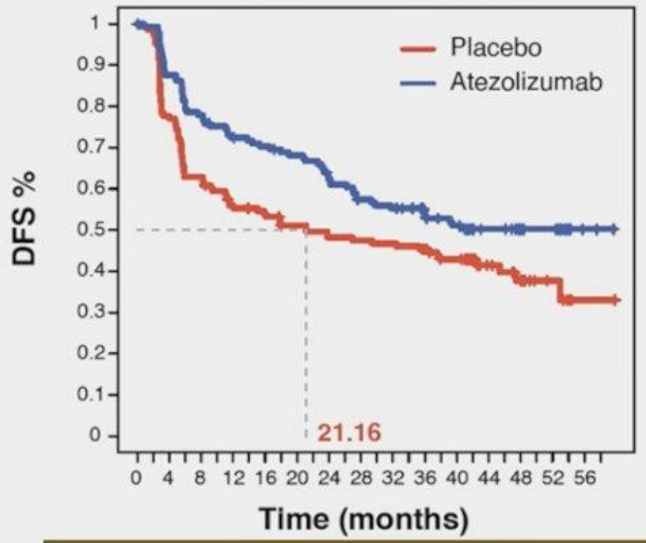

Disease Free Survival by Investigator (%)
100
90
80
70
60
50
40
30
20
10
0
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60
Time (Months)
Atezolizumab (n=390)
Placebo (n=388)
DFS events, n (%)[a] 164 (42) 168 (43)
Median (95% CI), mo 57.2 (44.6, NE) 49.5 (47.4, NE)
Stratified HR (95% CI) 0.93 (0.75, 1.15); P=0.4950[b]
Patients remaining at risk
Placebo 388 343 305 294 275 268 254 243 232 226 216 209 187 161 121 91 56 33 15 3 NE
Atezolizumab 390 360 322 306 288 272 265 257 244 234 222 218 194 171 124 100 75 48 22 6 1





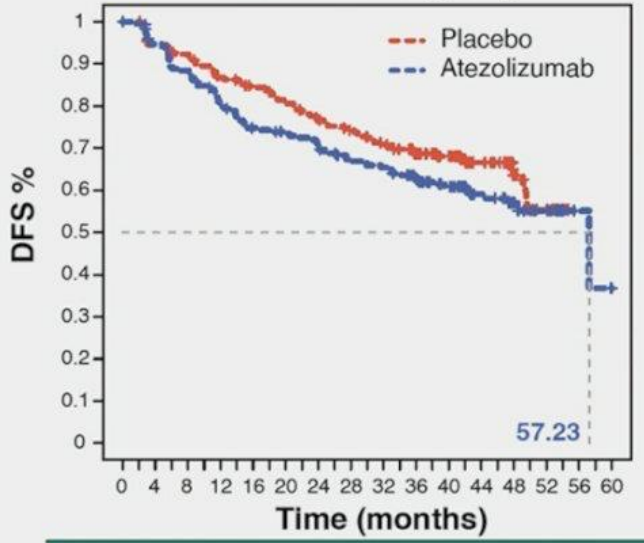
Baseline

KIM-1^{High} subgroup



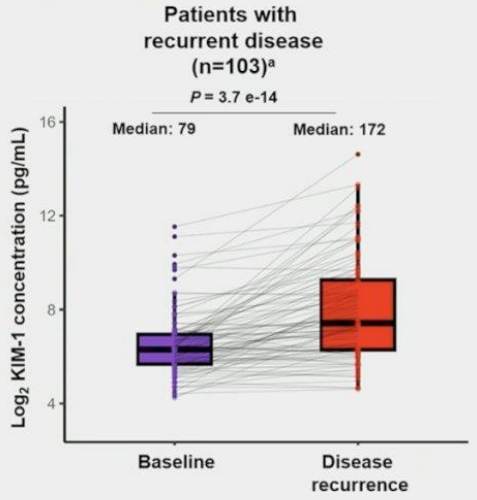
	n	Median DFS	HR[a] (95% CI)
Atezolizumab	151	NE	0.72 (0.52, 0.99)
Placebo	149	21.16	

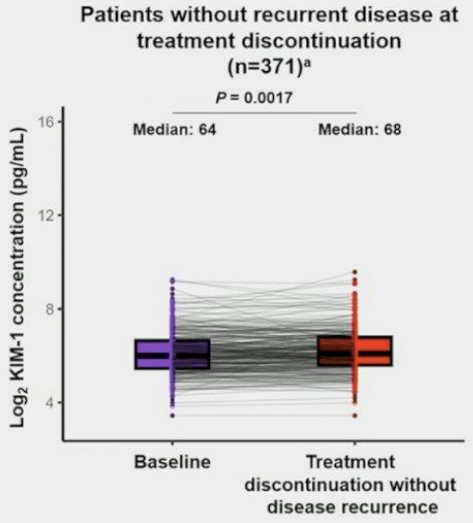
KIM-1^{Low} subgroup



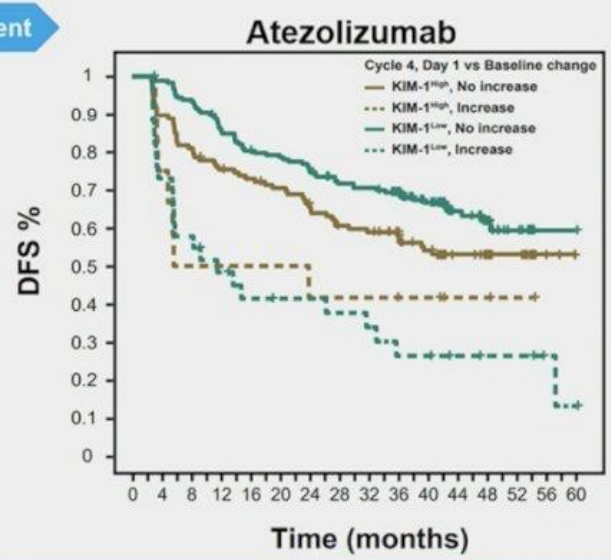
	n	Median DFS	HR[a] (95% CI)
Atezolizumab	229	57.23	1.12 (0.88, 1.63)
Placebo	223	NE	

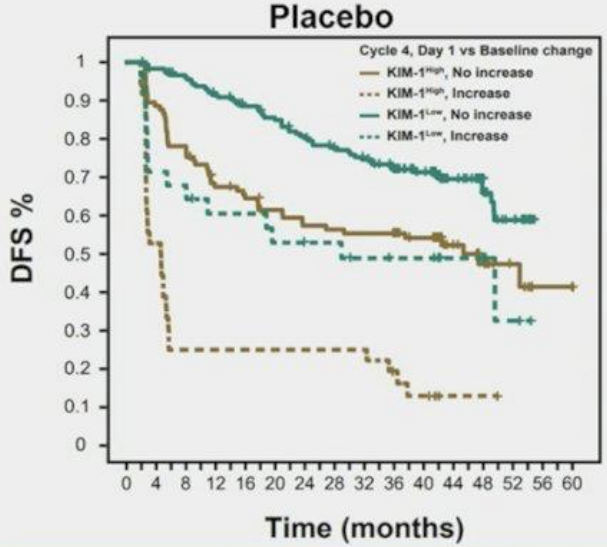
Disease Recurrence/ Treatment Discontinuation





On Treatment





Baseline	On-treatment	n	Median DFS	HR (95% CI)
KIM-1^{High}	Increase[a]	12	14.8	1.68 (0.77, 3.69)
	No increase	126	NE	
KIM-1^{Low}	Increase[a]	34	11.5	3.56 (2.21, 5.75)
	No increase	179	NE	

Baseline	On-treatment	n	Median DFS	HR (95% CI)
KIM-1^{High}	Increase[a]	36	4.8	3.53 (2.24, 5.58)
	No increase	105	45.4	
KIM-1^{Low}	Increase[a]	28	29.0	2.51 (1.42, 4.44)
	No increase	179	NE	

Takeaways:

- In IMmotion010, high baseline serum levels of KIM-1 were associated with worse prognosis but better clinical outcomes with Atezo vs. placebo.
- Increased post-Tx KIM-1 levels were associated with worse DFS.
- Need for additional validation studies of KIM-1 as a biomarker in ccRCC.

Questions????