6th Knowledge Series For Genitourinary Cancers Best of 2024

KIMS HOSPITALS™

RENOTORCH

Toripalimab plus axitinib versus sunitinib as first-line treatment for advanced renal cell carcinoma

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Bone marrow Transplant physician

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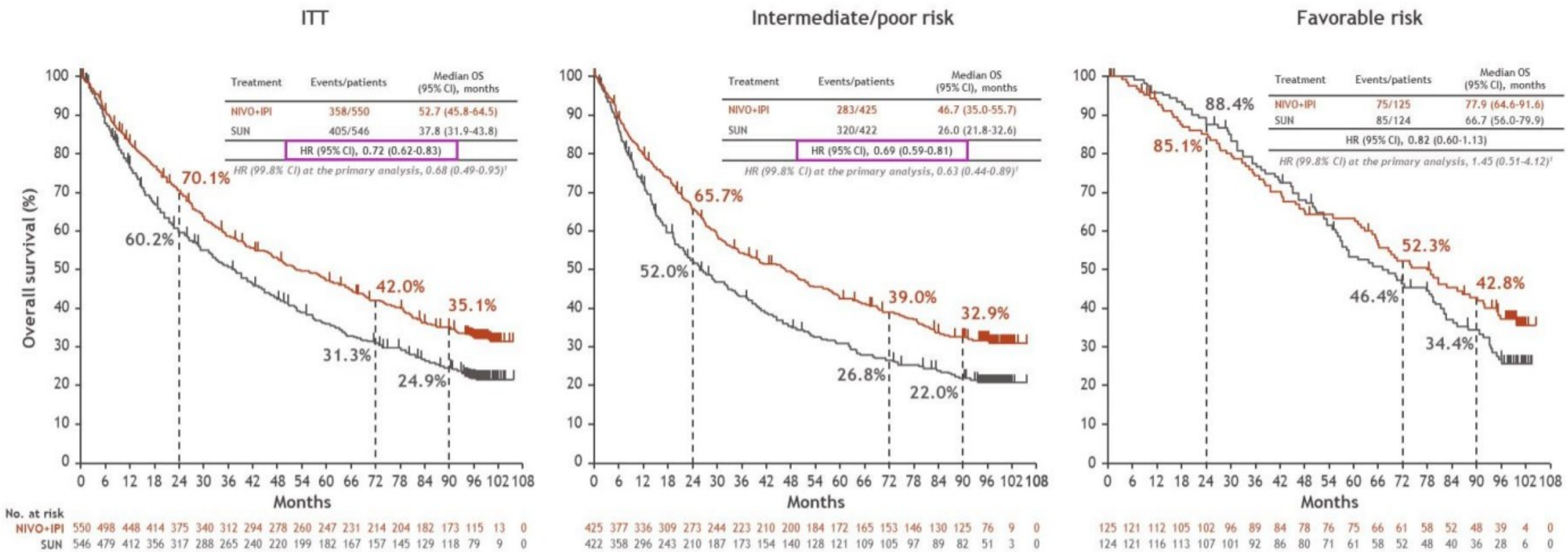
How other drugs performed

	SUNITINIB [control arm range] from 4 pivotal phase 3 trials	Nivolumab + Ipilimumab n=550	Pembrolizumab + Axitinib n=432	Nivolumab + Cabozantinib N=323	Pembrolizumab + Lenvatinib n=355
Follow-up, mo (median)	**[44-68]**	**68**	**67**	**44**	**49**
Median PFS, mo	[8.4-12.3]	12.3	15.7	16.6	23.9
PFS HR vs SUNI		0.86	0.69	0.59	0.47
Median OS, mo	[35.5-54.3]	55.7	47.2	49.5	53.7
OS HR vs SUNI		0.72	0.84	0.70	0.79
ORR, %	[28-40]	39	61	56	71
CR, %	[3-5]	12	12	13	18
PD, %	[14-17]	18	12	7	5

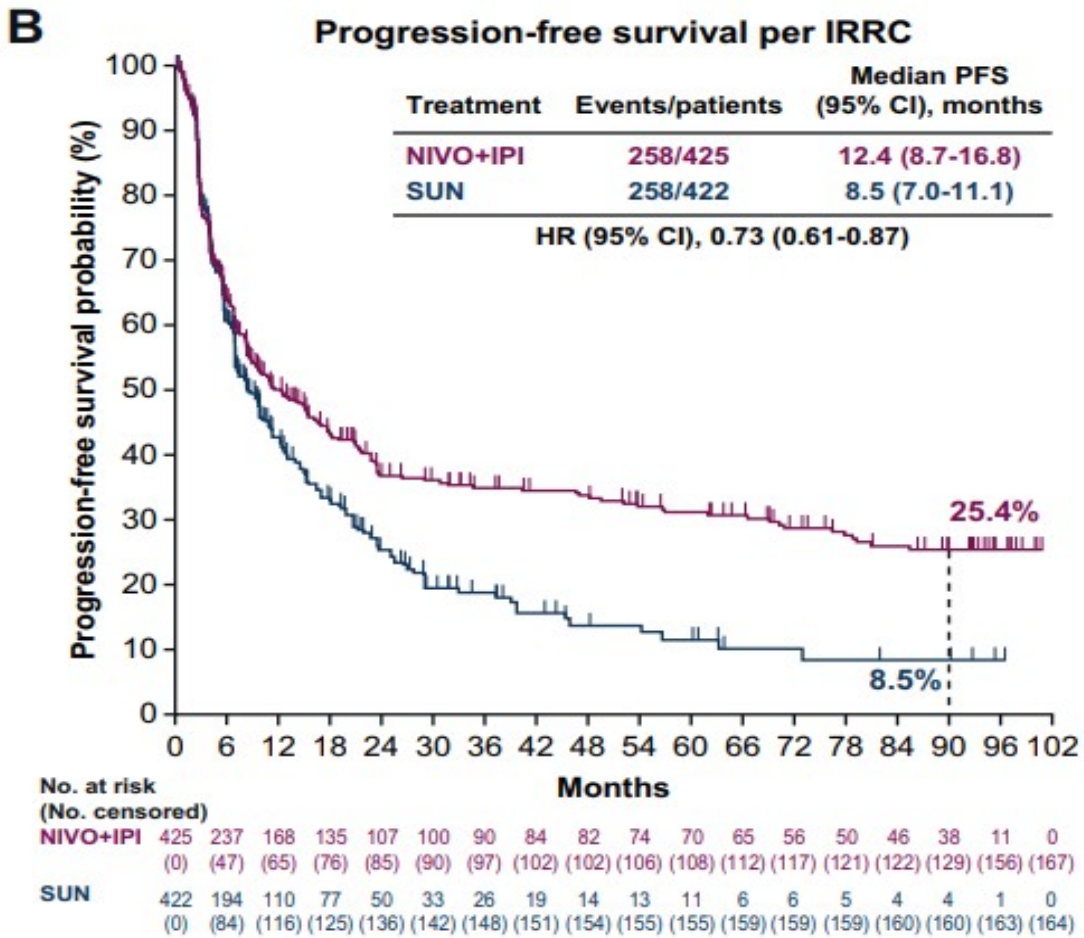
Motzer et al Cancer 2022 ; Rini et al. ASCO 2023 ; Burrotto et al. ASCOGU 2023 ; Motzer et al. ASCO 2023

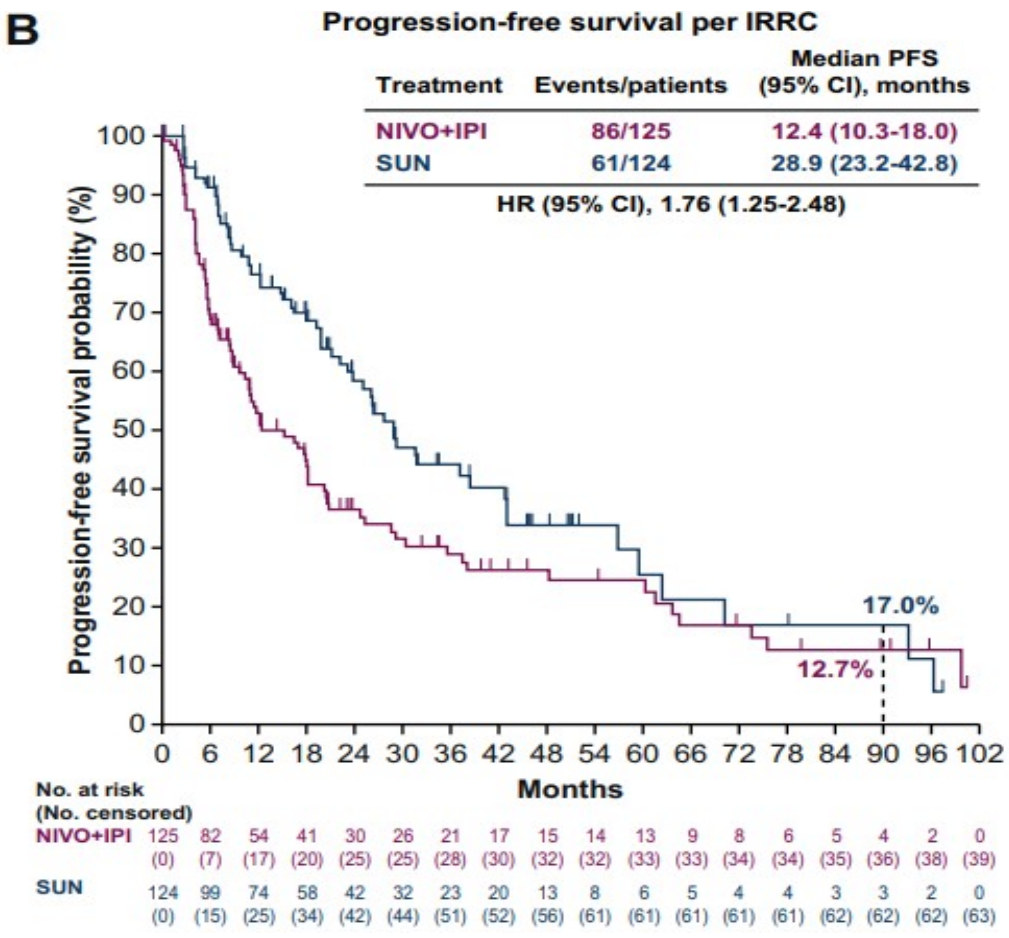
CheckMate 214 , OS



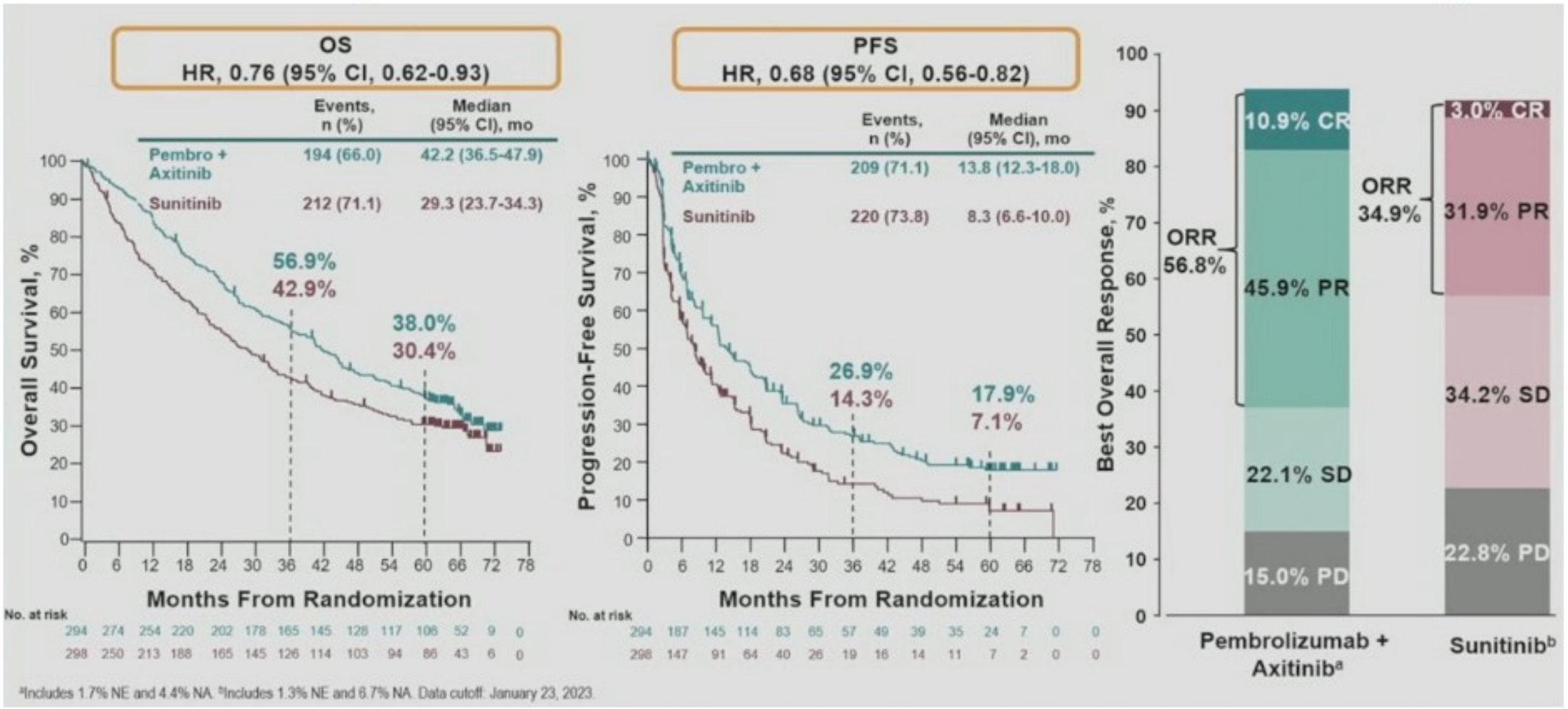
Tannir et al, ASCO GU 2024

CheckMate 214 ,PFS

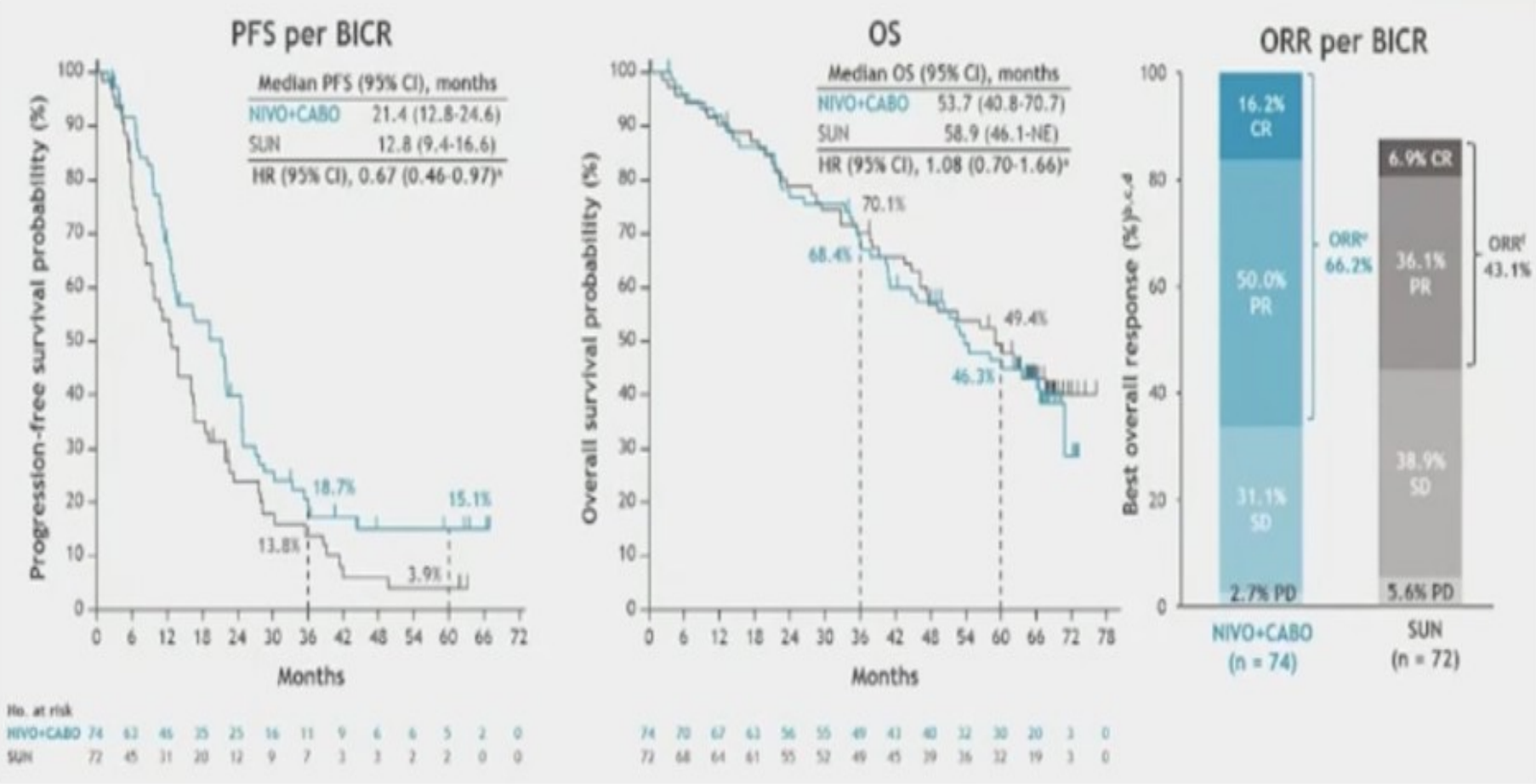




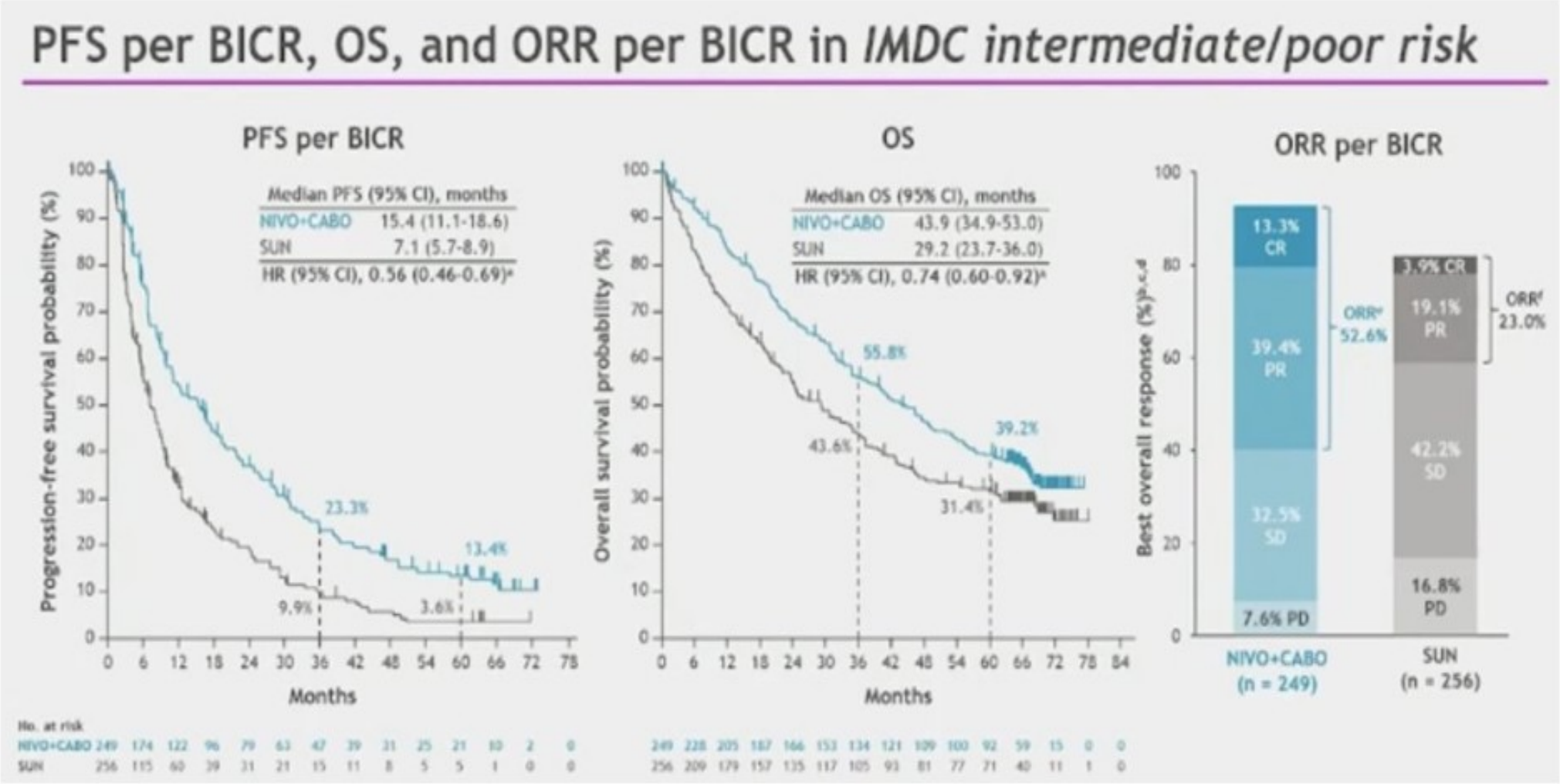
Keynote 426 , intermediate/poor risk



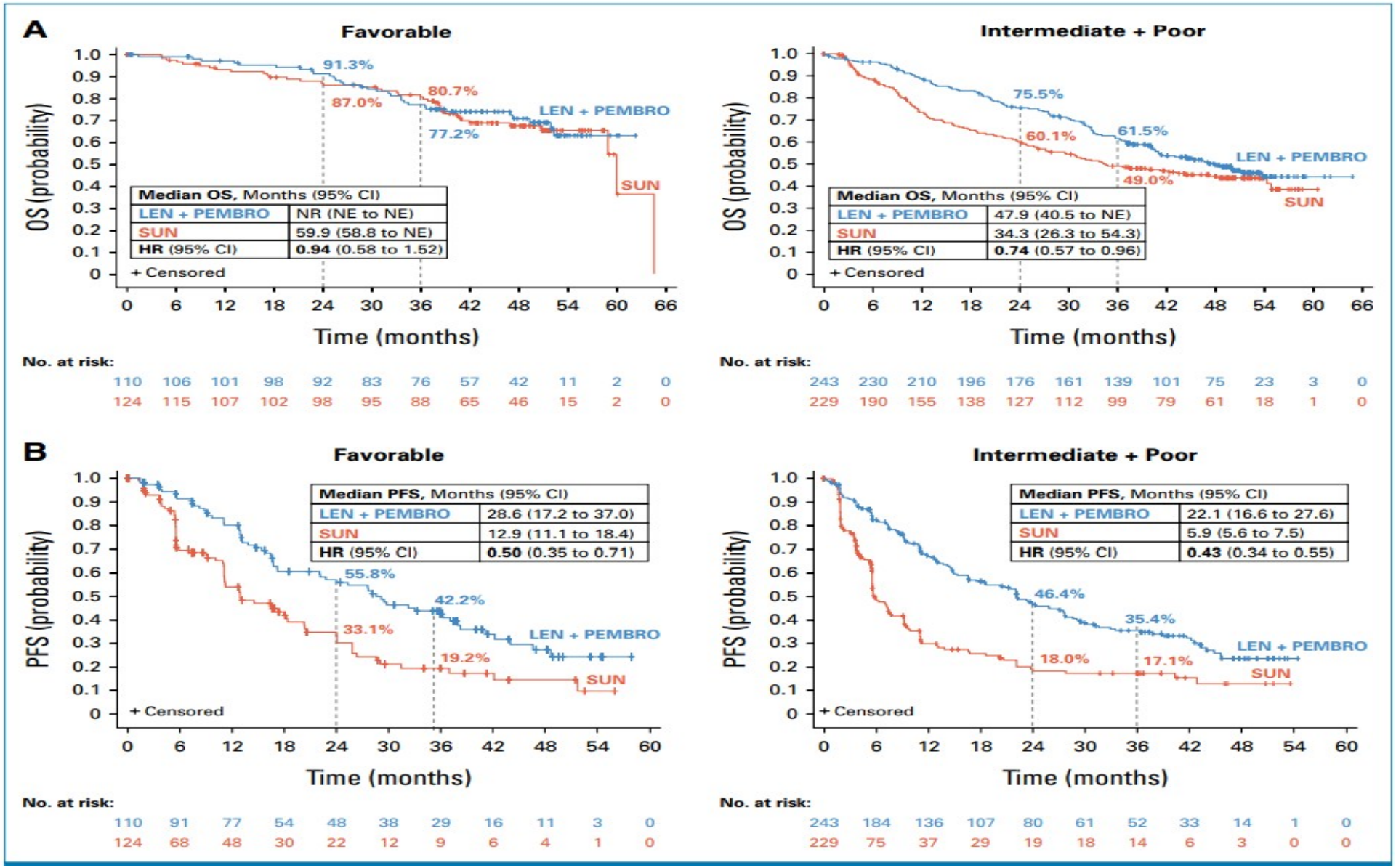
CheckMate 9 ER , favourable risk



CheckMate 9 ER , intermediate/ poor risk



Clear trial


A
Favorable
OS (probability)
Time (months)
91.3%
87.0%
80.7%
77.2%
LEN + PEMBRO
SUN
Median OS, Months (95% CI)
LEN + PEMBRO NR (NE to NE)
SUN 59.9 (58.8 to NE)
HR (95% CI) 0.94 (0.58 to 1.52)
+ Censored
No. at risk:
110 106 101 98 92 83 76 57 42 11 2 0
124 115 107 102 98 95 88 65 46 15 2 0
Intermediate + Poor
OS (probability)
Time (months)
75.5%
60.1%
61.5%
49.0%
LEN + PEMBRO
SUN
Median OS, Months (95% CI)
LEN + PEMBRO 47.9 (40.5 to NE)
SUN 34.3 (26.3 to 54.3)
HR (95% CI) 0.74 (0.57 to 0.96)
+ Censored
No. at risk:
243 230 210 196 176 161 139 101 75 23 3 0
229 190 155 138 127 112 99 79 61 18 1 0
B
Favorable
PFS (probability)
Time (months)
55.8%
42.2%
33.1%
19.2%
LEN + PEMBRO
SUN
Median PFS, Months (95% CI)
LEN + PEMBRO 28.6 (17.2 to 37.0)
SUN 12.9 (11.1 to 18.4)
HR (95% CI) 0.50 (0.35 to 0.71)
+ Censored
No. at risk:
110 91 77 54 48 38 29 16 11 3 0
124 68 48 30 22 12 9 6 4 1 0
Intermediate + Poor
PFS (probability)
Time (months)
46.4%
35.4%
18.0%
17.1%
LEN + PEMBRO
SUN
Median PFS, Months (95% CI)
LEN + PEMBRO 22.1 (16.6 to 27.6)
SUN 5.9 (5.6 to 7.5)
HR (95% CI) 0.43 (0.34 to 0.55)
+ Censored
No. at risk:
243 184 136 107 80 61 52 33 14 1 0
229 75 37 29 19 18 14 6 3 0 0

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Toripalimab plus axitinib versus sunitinib as first-line treatment for advanced renal cell carcinoma: RENOTORCH, a randomized, open-label, phase III study

X. Q. Yan[1†], M. J. Ye[2†], Q. Zou[3†], P. Chen[4], Z. S. He[5], B. Wu[6], D. L. He[7], C. H. He[8], X. Y. Xue[9], Z. G. Ji[10], H. Chen[11], S. Zhang[12], Y. P. Liu[13], X. D. Zhang[14], C. Fu[15], D. F. Xu[16], M. X. Qiu[17], J. J. Lv[18], J. Huang[19], X. B. Ren[20], Y. Cheng[21], W. J. Qin[22], X. Zhang[23], F. J. Zhou[24], L. L. Ma[25], J. M. Guo[26], D. G. Ding[27], S. Z. Wei[28], Y. He[29], H. Q. Guo[30], B. K. Shi[31], L. Liu[31], F. Liu[32], Z. Q. Hu[33], X. M. Jin[34], L. Yang[35], S. X. Zhu[36], J. H. Liu[37], Y. H. Huang[38], T. Xu[39], B. Liu[40], T. Sun[41], Z. J. Wang[42], H. W. Jiang[43], D. X. Yu[44], A. P. Zhou[45], J. Jiang[46], G. D. Luan[47], C. L. Jin[47], J. Xu[47], J. X. Hu[47], Y. R. Huang[48], J. Guo[1], W. Zhai[48*] & X. N. Sheng[1*]

Inclusion criteria

- Age between 18 to 80 years
- Histologically unresectable or metastatic clear cell RCC
- No previous systematic therapy (except cytokine treatment) for metastatic disease, at least one measurable lesion
- Intermediate or poor risk by IMDC classification
- Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1

Exclusion criteria

- Active central nervous system metastases .
- Active autoimmune disease, received systemic treatment with either glucocorticoids (>10 mg of prednisone equivalent per day) or other immunosuppressive medications within 14 days before the first dosing of study treatment .
- Poorly controlled hypertension (systolic blood pressure 150 mm Hg or diastolic blood pressure 90mm Hg) .

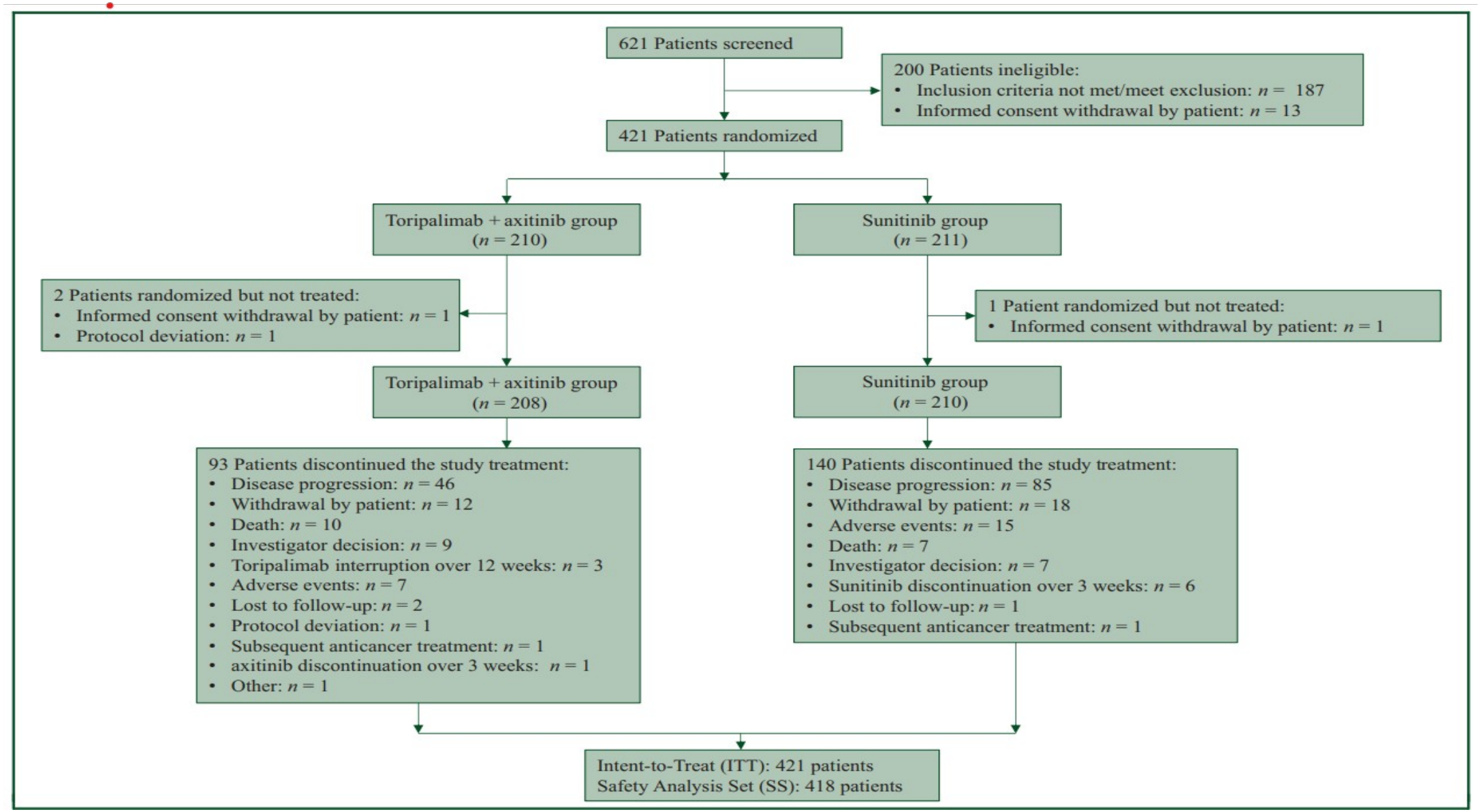

621 Patients screened
200 Patients ineligible:
• Inclusion criteria not met/meet exclusion: n = 187
• Informed consent withdrawal by patient: n = 13
421 Patients randomized
Toripalimab + axitinib group (n = 210)
Sunitinib group (n = 211)
2 Patients randomized but not treated:
• Informed consent withdrawal by patient: n = 1
• Protocol deviation: n = 1
1 Patient randomized but not treated:
• Informed consent withdrawal by patient: n = 1
Toripalimab + axitinib group (n = 208)
Sunitinib group (n = 210)
93 Patients discontinued the study treatment:
• Disease progression: n = 46
• Withdrawal by patient: n = 12
• Death: n = 10
• Investigator decision: n = 9
• Toripalimab interruption over 12 weeks: n = 3
• Adverse events: n = 7
• Lost to follow-up: n = 2
• Protocol deviation: n = 1
• Subsequent anticancer treatment: n = 1
• axitinib discontinuation over 3 weeks: n = 1
• Other: n = 1
140 Patients discontinued the study treatment:
• Disease progression: n = 85
• Withdrawal by patient: n = 18
• Adverse events: n = 15
• Death: n = 7
• Investigator decision: n = 7
• Sunitinib discontinuation over 3 weeks: n = 6
• Lost to follow-up: n = 1
• Subsequent anticancer treatment: n = 1
Intent-to-Treat (ITT): 421 patients
Safety Analysis Set (SS): 418 patients

Table 1. Demographic and other baseline characteristics (intent-to-treat population)

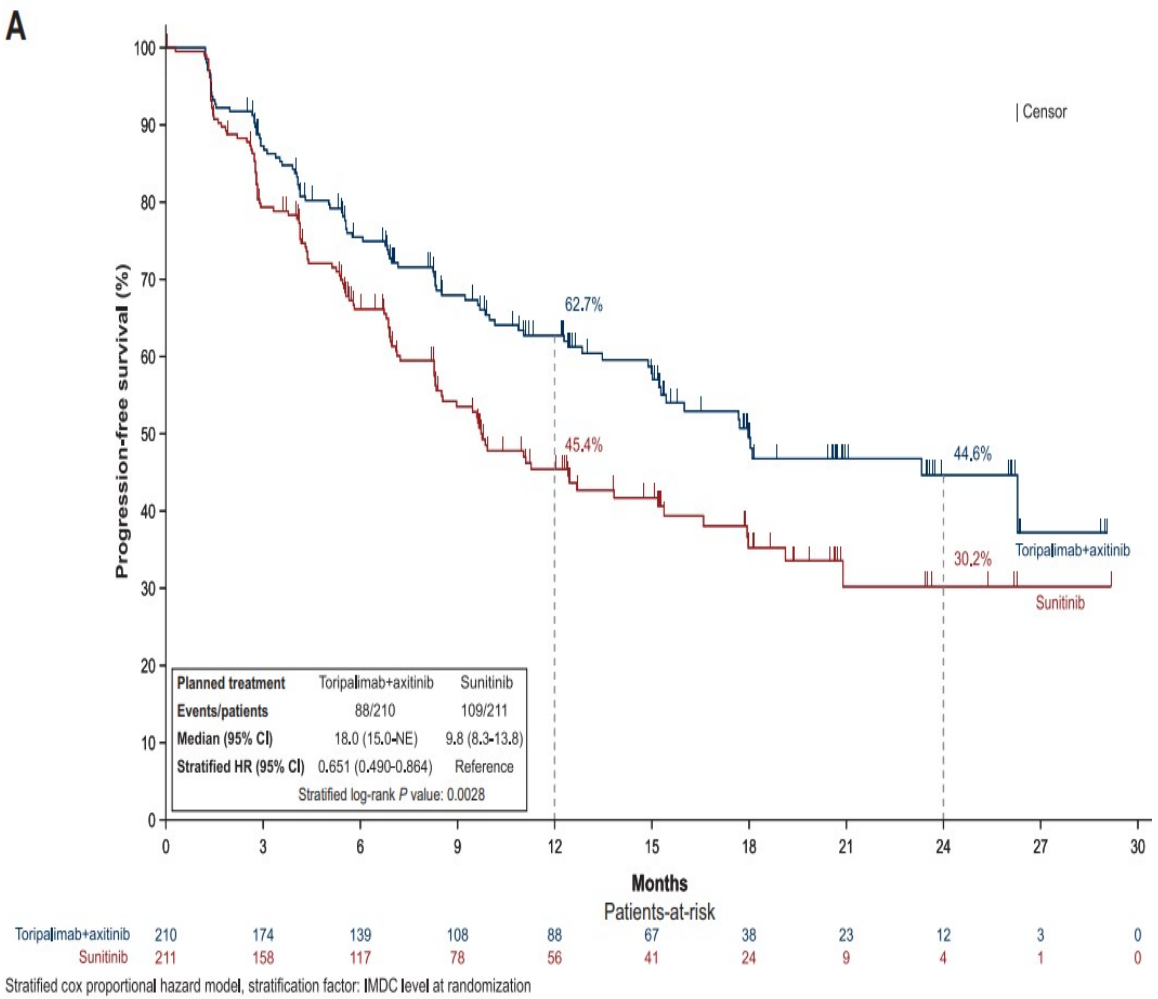
Characteristics	Toripalimab + axitinib (*n* = 210)	Sunitinib (*n* = 211)	Total (*n* = 421)
Age (years)			
Median (range)	60.0 (20-78)	60.0 (28-78)	60.0 (20-78)
Age categories (years), *n* (%)			
<65	135 (64.3)	148 (70.1)	283 (67.2)
≥65	75 (35.7)	63 (29.9)	138 (32.8)
Sex, *n* (%)			
Male	162 (77.1)	157 (74.4)	319 (75.8)
Female	48 (22.9)	54 (25.6)	102 (24.2)
ECOG performance status, *n* (%)			
0	109 (51.9)	109 (51.7)	218 (51.8)
1	101 (48.1)	102 (48.3)	203 (48.2)
KPS, *n* (%)			
100-90	121 (57.6)	118 (55.9)	239 (56.8)
80-70	89 (42.4)	93 (44.1)	182 (43.2)
IMDC risk group, *n* (%)			
Intermediate	169 (80.5)	174 (82.5)	343 (81.5)
Poor	41 (19.5)	37 (17.5)	78 (18.5)
Number of organs with metastases, *n* (%)			
0	9 (4.3)	8 (3.8)	17 (4.0)
1	63 (30.0)	84 (39.8)	147 (34.9)
≥2	138 (65.7)	119 (56.4)	257 (61.0)
Site of metastasis, *n* (%)			
Lung	152 (72.4)	137 (64.9)	289 (68.6)
Liver	34 (16.2)	31 (14.7)	65 (15.4)
Bone	48 (22.9)	43 (20.4)	91 (21.6)
Previous nephrectomy, *n* (%)			
Yes	135 (64.3)	127 (60.2)	262 (62.2)
No	75 (35.7)	84 (39.8)	159 (37.8)

Response Rates

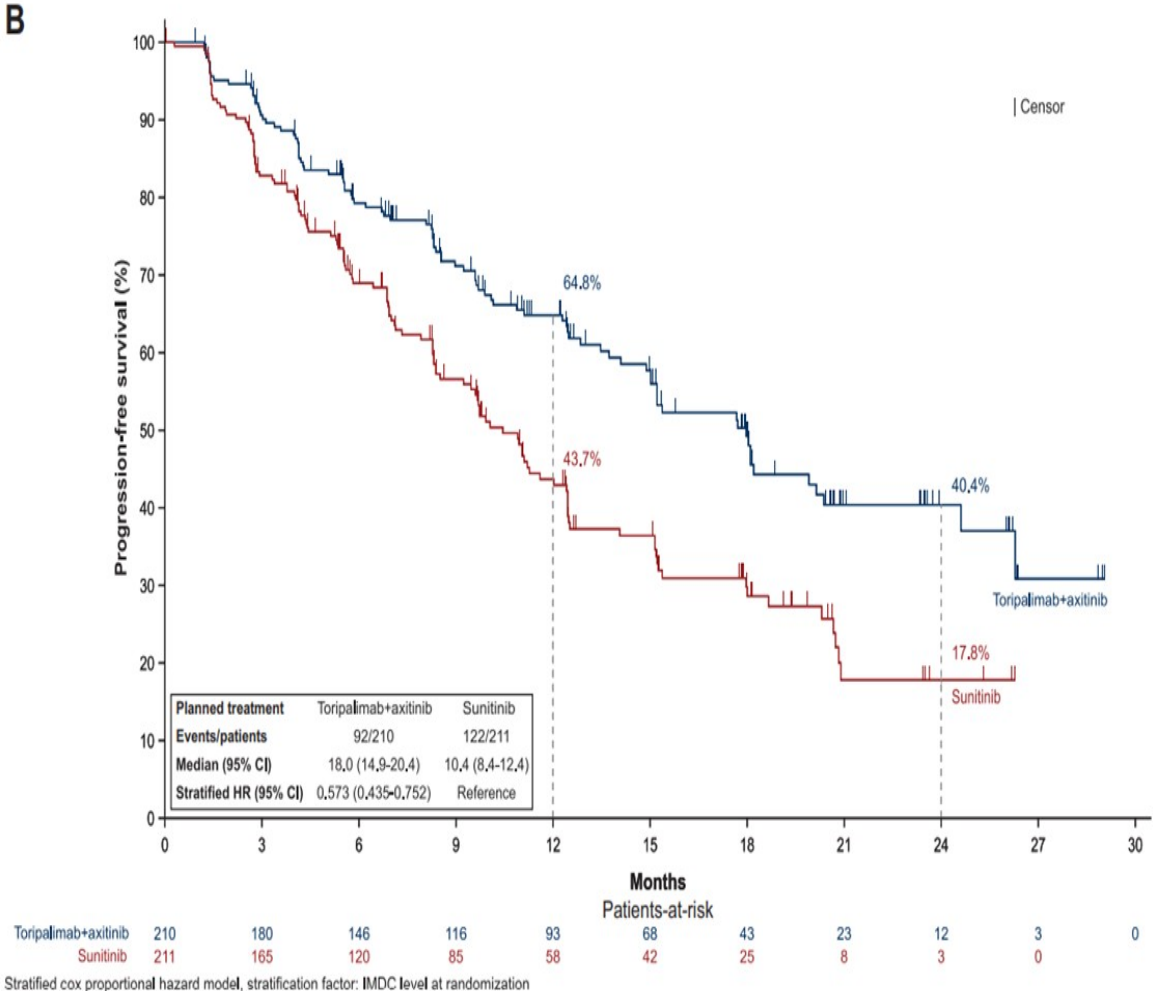
Table 2. Summary of tumor response assessed by the IRC and investigators according to RECIST version 1.1 (intent-to-treat population)

Variables	IRC assessed		Investigator assessed	
	Toripalimab + axitinib (n = 210)	Sunitinib (n = 211)	Toripalimab + axitinib (n = 210)	Sunitinib (n = 211)
Best overall response, n (%)				
Complete response	10 (4.8)	8 (3.8)	4 (1.9)	2 (0.9)
Partial response	109 (51.9)	57 (27.0)	118 (56.2)	63 (29.9)
Stable disease	61 (29.0)	106 (50.2)	66 (31.4)	109 (51.7)
Noncomplete response/nonprogressive disease	2 (1.0)	1 (0.5)	—	—
Progressive disease	22 (10.5)	29 (13.7)	15 (7.1)	25 (11.8)
Not evaluable	1 (0.5)	1 (0.5)	2 (1.0)	3 (1.4)
Not assessed	5 (2.4)	9 (4.3)	5 (2.4)	9 (4.3)
Objective response rate, n (%)	119 (56.7)	65 (30.8)	122 (58.1)	65 (30.8)
95% CI[a]	49.7-63.5	24.6-37.5	51.1-64.8	24.6-37.5
P value	<0.0001			
Disease control rate, n (%)	182 (86.7)	172 (81.5)	188 (89.5)	174 (82.5)
95% CI	81.3-91.0	75.6-86.5	84.6-93.3	76.6-87.3
Median duration to response[b] (range)	NE (0.0-27.9)	16.7 (0.0-24.9)	23.2 (0.0-27.6)	13.8 (0.0-23.5)

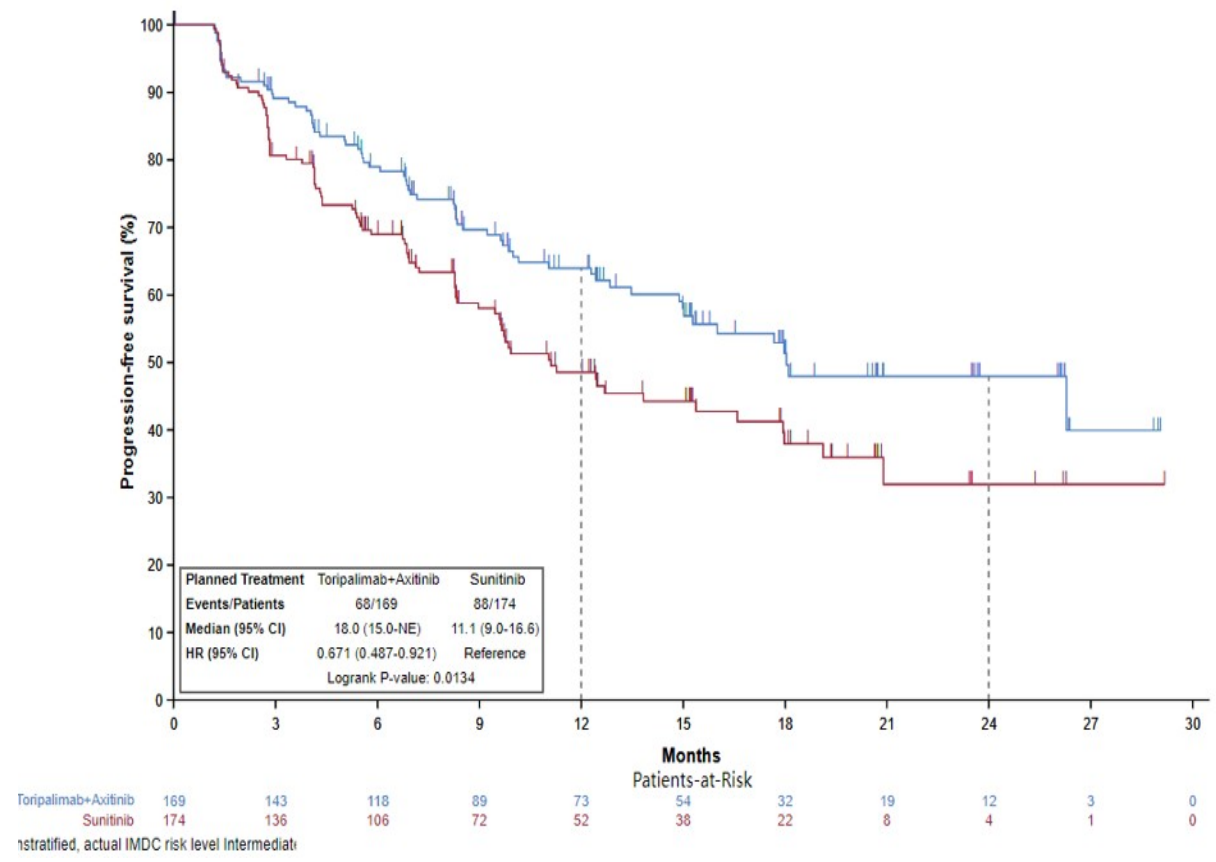
IRC PFS



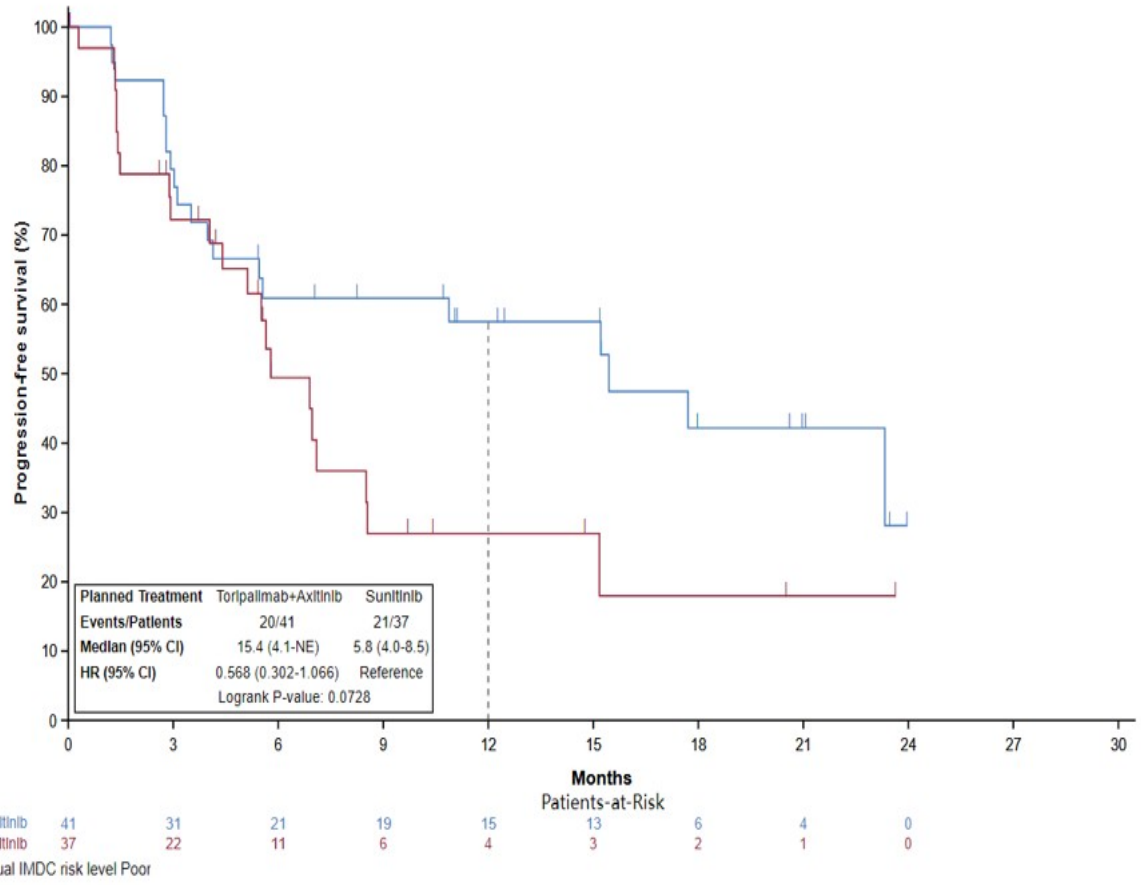
INVESTIGATOR PFS



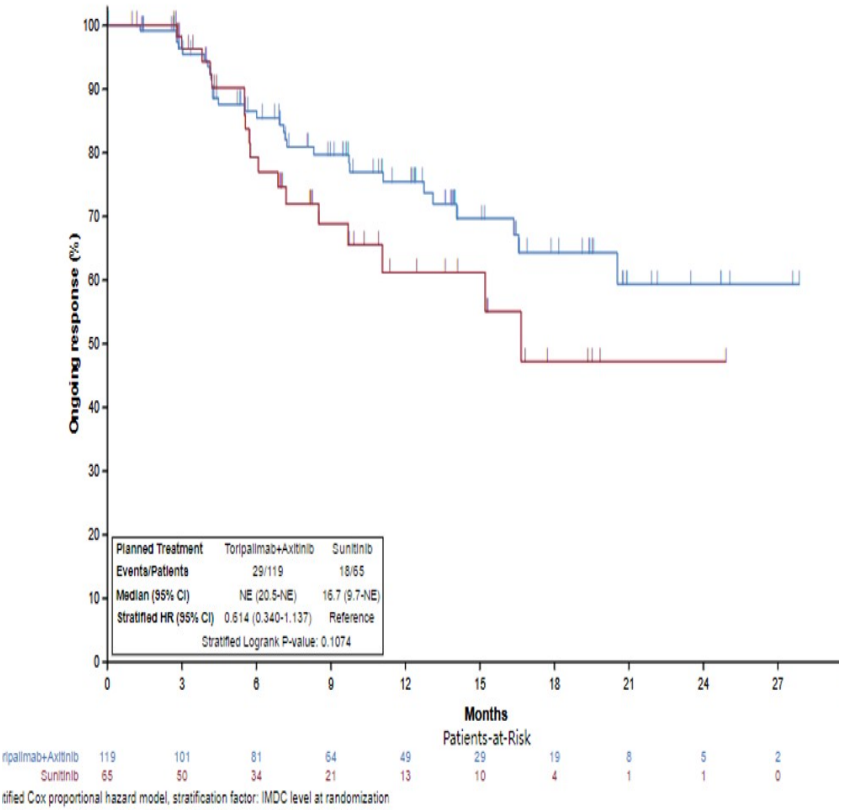
Intermediate Risk



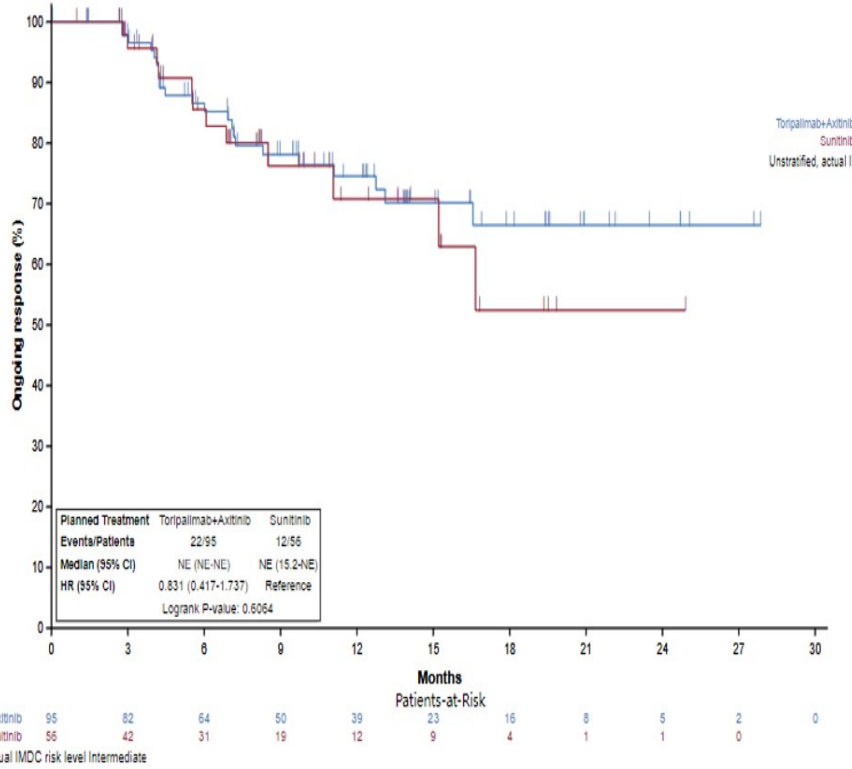
Poor Risk



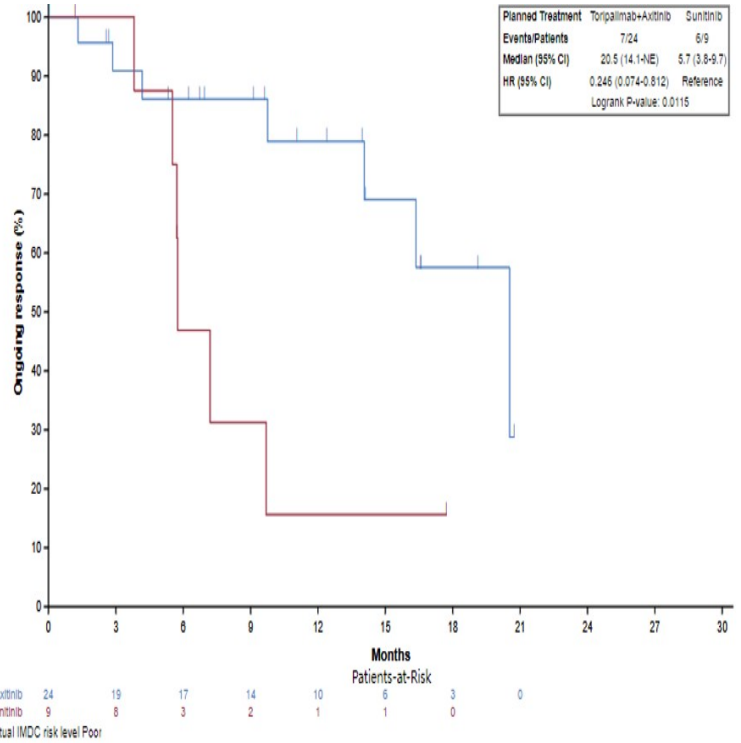
Duration of Response



tified Cox proportional hazard model, stratification factor: IMDC level at randomization

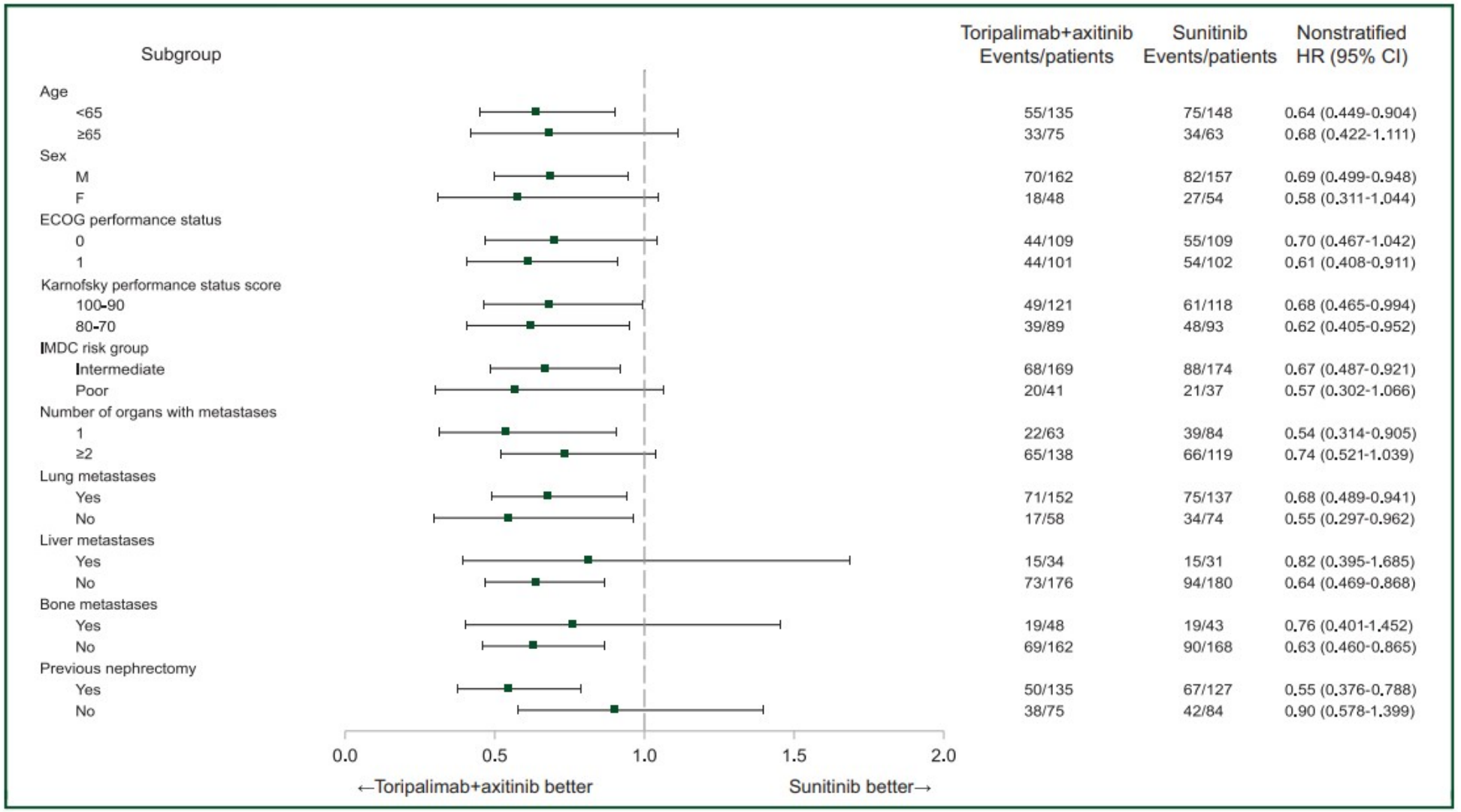


Unstratified, actual IMDC risk level Intermediate

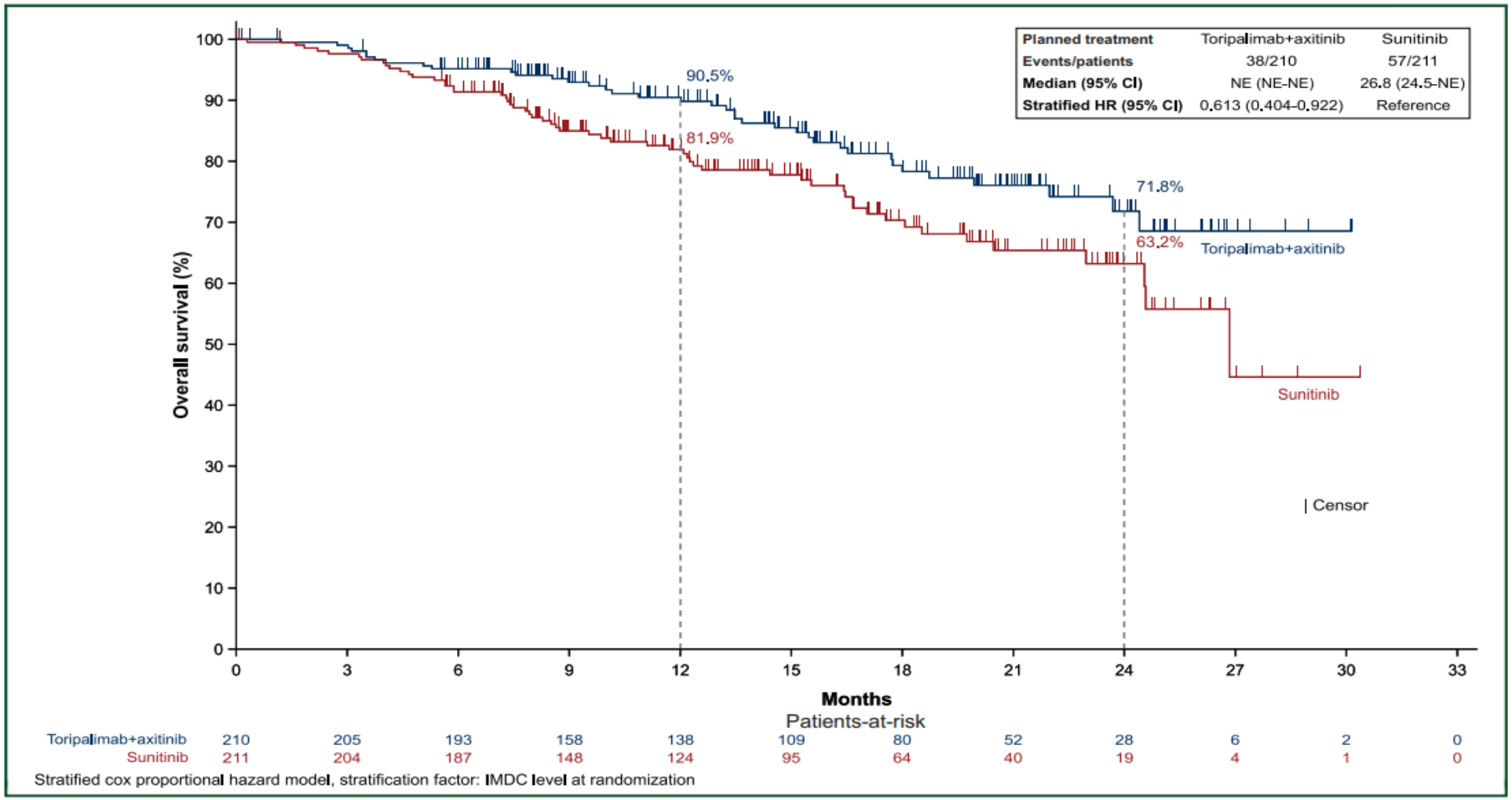


Unstratified, actual IMDC risk level Poor

Subgroup analysis – PFS



OVERALL SURVIVAL



Subsequent anticancer treatment

Table S1. Subsequent New Anti-Cancer Therapy

	Toripalimab + Axitinib *N*=93 *n* (%)	Sunitinib *N*=140 *n* (%)	Total *N*=233 *n* (%)
Number of Patients Who Received Subsequent Anti-Tumor Drugs	34 (36.6)	71 (50.7)	105 (45.1)
PD-1/PD-L1 inhibitor	11 (11.8)	37 (26.4)	48 (20.6)
VEGF(R) inhibitor	31 (33.3)	60 (42.9)	91 (39.1)
mTOR inhibitor	7 (7.5)	3 (2.1)	10 (4.1)
CTLA inhibitor	1 (1.1)	0	1 (0.4)
Other	3 (3.2)	14 (10.0)	17 (7.3)

The denominator is the number of patients who discontinued the study treatment.

PD-1 = programmed cell death -1; PD-L1 = programmed cell death ligand -1; VEGF(R) = vascular endothelial growth factor (receptor); mTOR= mammalian target of rapamycin; CTLA = cytolytic T lymphocyte-associated antigen

Overall TEAE

	Toripalimab + Axitinib *N*=208 *n* (%)	Sunitinib *N*=210 *n* (%)
TEAE	207 (99.5)	209 (99.5)
Related to any study treatment	203 (97.6)	205 (97.6)
Related to axitinib	200 (96.2)	0
Related to toripalimab	192 (92.3)	0
Related to toripaliamb and axitinib*	178 (85.6)	0
CTCAE Grade ≥ 3 TEAE	148 (71.2)	141 (67.1)
Related to any study treatment	128 (61.5)	123 (58.6)
Related to axitinib	122 (58.7)	0
Related to toripalimab	95 (45.7)	0
Related to toripaliamb and axitinib	82 (39.4)	0
SAE	93 (44.7)	60 (28.6)
Related to any study treatment	59 (28.4)	35 (16.7)
Related to axitinib	48 (23.1)	0
Related to toripalimab	48 (23.1)	0
Related to toripaliamb and axitinib	35 (16.8)	0
TEAEs leading to study treatment interruption	144 (69.2)	91 (43.3)
Axitinib interruption	113 (54.3)	0
Toripalimab interruption	123 (59.1)	0
Axitinib and toripalimab interruption	83 (39.9)	0
Related to any study treatment	119 (57.2)	82 (39.0)
Related to axitinib	105 (50.5)	0
Related to toripalimab	97 (46.6)	0
Related to toripaliamb and axitinib	81 (38.9)	0
TEAEs leading to study treatment discontinuation	30 (14.4)	17 (8.1)
Axitinib discontinuation	9 (4.3)	0
Toripalimab discontinuation	27 (13.0)	0
Axitinib and toripalimab discontinuation	4 (1.9)	0
Related to any study treatment	25 (12.0)	12 (5.7)
Related to axitinib	21 (10.1)	0
Related to toripalimab	24 (11.5)	0
Related to toripaliamb and axitinib	19 (9.1)	0
TEAEs leading to dose reduction of axitinib/sunitinib	65 (31.3)	57 (27.1)
Related to any study treatment	65 (31.3)	55 (26.2)
Related to axitinib	65 (31.3)	0
Related to toripalimab	40 (19.2)	0
Related to toripaliamb and axitinib	40 (19.2)	0
Fata TEAE	8 (3.8)	5 (2.4)
Related to any study treatment	2 (1.0)	2 (1.0)
Related to axitinib	2 (1.0)	0
Related to toripalimab	2 (1.0)	0
Related to toripaliamb and axitinib	2 (1.0)	0
Immune-related adverse events (irAE)	73 (35.1)	1 (0.5)
CTCAE Grade ≥3	30 (14.4)	0

*Discontinuation of both drugs concurrently by the same AE at the same time

Fatal Adverse events

Table S5. Fatal Adverse Events (Safety Analysis Set)

Preferred Term	Toripalimab + Axitinib *N*=208 *n* (%)	Sunitinib *N*=210 *n* (%)
TEAEs with an outcome of death	8 (3.8)	5 (2.4)
Sudden cardiac death	2 (1.0)	0
Death	1 (0.5)	4 (1.9)
COVID-19 pneumonitis	1 (0.5)	0
Infection	1 (0.5)	0
Pneumonitis	1 (0.5)	0
Ketoacidosis	1 (0.5)	0
Cerebral haemorrhage	1 (0.5)	0
Bronchial haemorrhage	1 (0.5)	0
Anal abscess	0	1 (0.5)

IRAE with an incidence of more than 1 % in experimental arm

Table S6. Immune-Related Adverse Events with an Incidence ≥ 1% in the Toripalimab-axitinib group (Safety Analysis Set)

Preferred Term	Toripalimab + Axitinib *N*=208 *n* (%)
Any irAEs	73 (35.1)
Hypothyroidism	21 (10.1)
Hyperthyroidism	13 (6.3)
Rash	10 (4.8)
Hepatic function abnormal	6 (2.9)
Diarrhoea	6 (2.9)
Adrenal insufficiency	5 (2.4)
Blood thyroid stimulating hormone increased	5 (2.4)
Blood creatinine increased	5 (2.4)
Immune-mediated pneumonitis	5 (2.4)
Hypophysitis	3 (1.4)
Aspartate aminotransferase increased	3 (1.4)
Protein urine present	3 (1.4)

Preferred Term	Toripalimab + Axitinib *N*=208 *n* (%)
Blood thyroid stimulating hormone decreased	3 (1.4)
Immune-mediated hepatic disorder	3 (1.4)
Immune-mediated hepatitis	3 (1.4)
Hyponatraemia	3 (1.4)
Asthenia	3 (1.4)
Pyrexia	3 (1.4)
Immune-mediated arthritis	3 (1.4)
Electroardiogram T wave abnormal	2 (1.0)
Tri-iodothyronine free increased	2 (1.0)
Thyroxine free decreased	2 (1.0)
Troponin T increased	2 (1.0)
Blood pressure increased	2 (1.0)
Blood creatine phosphokinase increased	2 (1.0)
Immune-mediated dermatitis	2 (1.0)
Blister	2 (1.0)

Comparison of efficacy and AE

Trial	Median OS	HR	Median PFS	HR	ORR	CR	Grade > 3 AE	Common AE
KEYNOTE 426	42	0.76	13	0.68	59.3	5	75%	HTN, Diarrhea, LFT alt Hypothyroidism
Checkmate9ER	43	0.74	15	0.56	55.7	13	67%	Diarrhea, Fatigue, HTN, HFS , LFT alt
CLEAR	47	0.74	22	0.43	71.3	18	82%	Diarrhea, HTN, Fatigue , appetite decrease
RENOTORCH	NE	0.61	18	0.65	56.7	4	71%	HTN, Diarrhea, Hepatotoxicity

Limitations

- Open label study
- Limited to one geographic area
- Patients above the 80 years were excluded
- Exclusion of favourable risk patients
- Short follow up
- No data on quality of life or patient reported outcomes
- Immature overall survival data

My take

- Almost equal overall response rates
- May be less CR rates compared to remaining ICI + TKI combinations
- Fairly doing on par with remaining ICI + TKI combinations with available follow up
- Needs to long term follow up data to look for OS benfit
- There is no hurry to adopt this combo in the tomorrow morning opd - over and above available regimens .

- This combo also will stay in the race , but may not won the race – time will decide

THANK YOU