Adjuvant treatment for high-risk clear cell renal cancer: hype or hope?

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Clinical Prognostic models to select for adjuvant therapy

Model	Type	Histology	Inclusion criteria (pathological stage)	Variables	Outcome
Cindolo[146,173]	Formula	Clear cell, papillary, chromophobe	T1–3 N0 M0	Tumour size, local symptoms	RFS
Karakiewicz[174]	Nomogram	Clear cell, papillary, chromophobe	T1–3 N0–2 M0–1	TNM[a], tumour size, Fuhrman grade, histological subtype, local symptoms, age, sex	CSS
Kattan[4]	Nomogram	Clear cell, papillary, chromophobe	T1–3 N0 M0	TNM[a], tumour size, histological subtype, local symptoms	RFS
Leibovich[135,145]	Algorithm	ccRCC	T(any) N0–2 M0	TNM[a], tumour size, positive node(s) Fuhrman grade, necrosis	MFS
MSKCC[175]	Nomogram	ccRCC	T1–3b N0 M0	TNM[a], tumour size, Fuhrman grade, necrosis, local symptoms	RFS
PRELANE[176]	Algorithm	Any	T(any) N0–1 M0	TNM[a], tumour size, positive node(s), histological subtype, Fuhrman grade, lymphovascular invasion, age, sex	RFS after 5 years
SSIGN[177]	Algorithm	ccRCC	T(any) N0–2 M0–1	TNM[a], tumour size, positive node(s), presence of metastases, Fuhrman grade, necrosis	CSS
UISS[178]	Kaplan–Meier analysis	Clear cell, papillary, chromophobe	T(any) N0–2 M0–1	TNM[a], Fuhrman grade, ECOG performance status	OS
Yaycioglu[179]	Formula	Clear cell, papillary, chromophobe	T1–3 N0 M0	Tumour size, local symptoms	RFS

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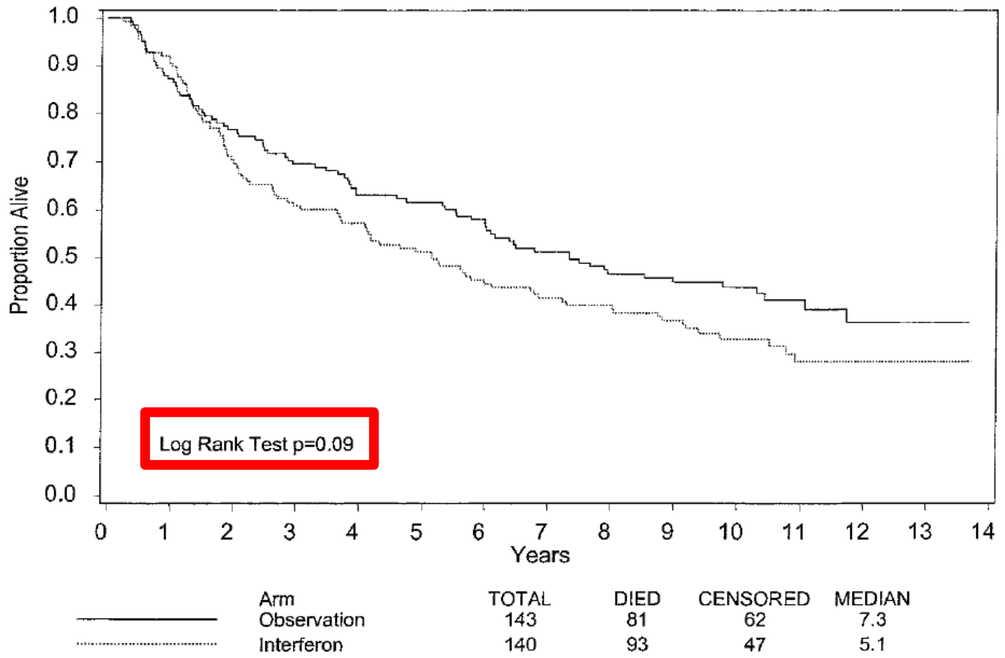
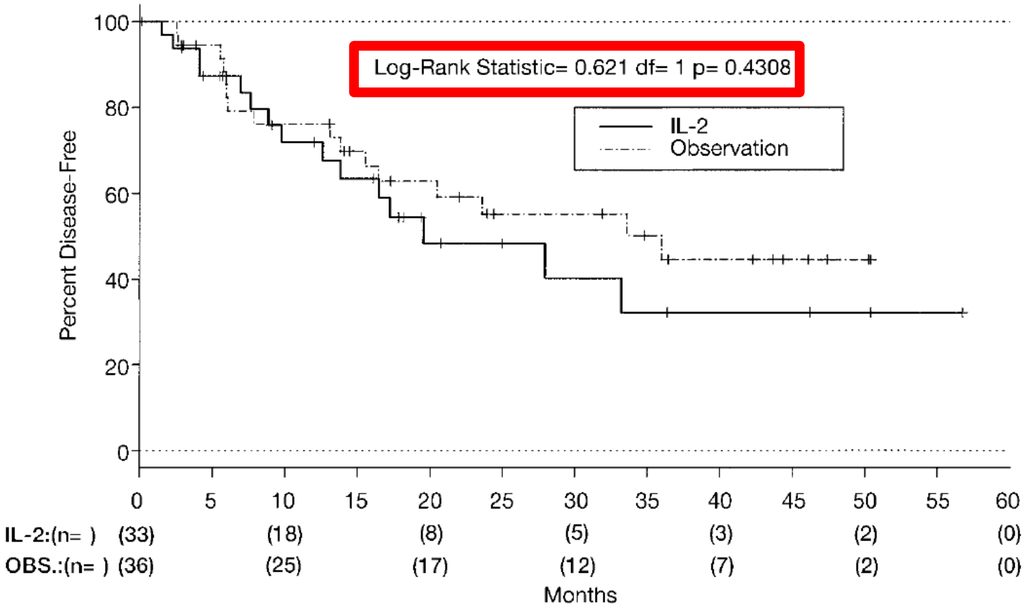
Cytokines as adjuvant therapy

IFN-α 2b



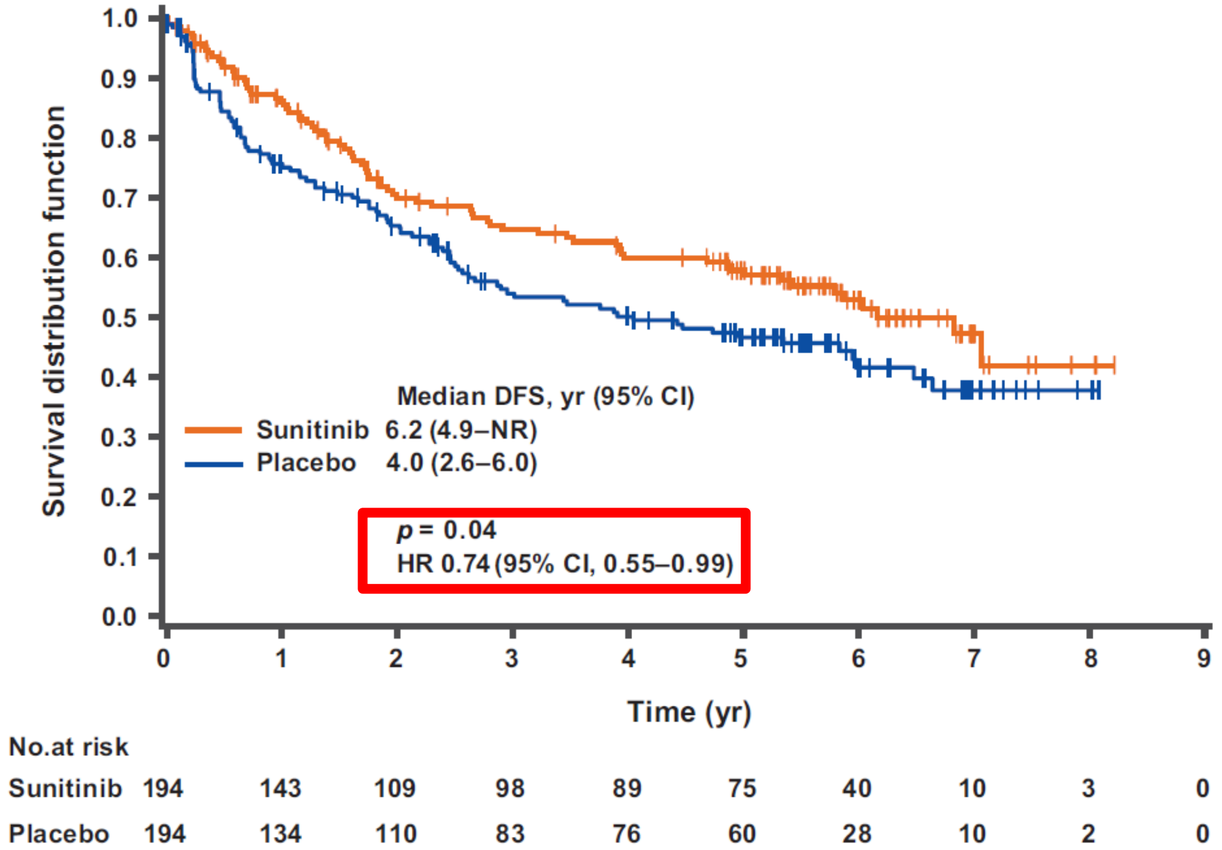
Messing EM, et al. J Clin Oncol 2003; 21:1214-1222.

High dose IL-2



Clark JI, et al. J Clin Oncol 2003; 2003 Aug 15;21(16):3133-40.

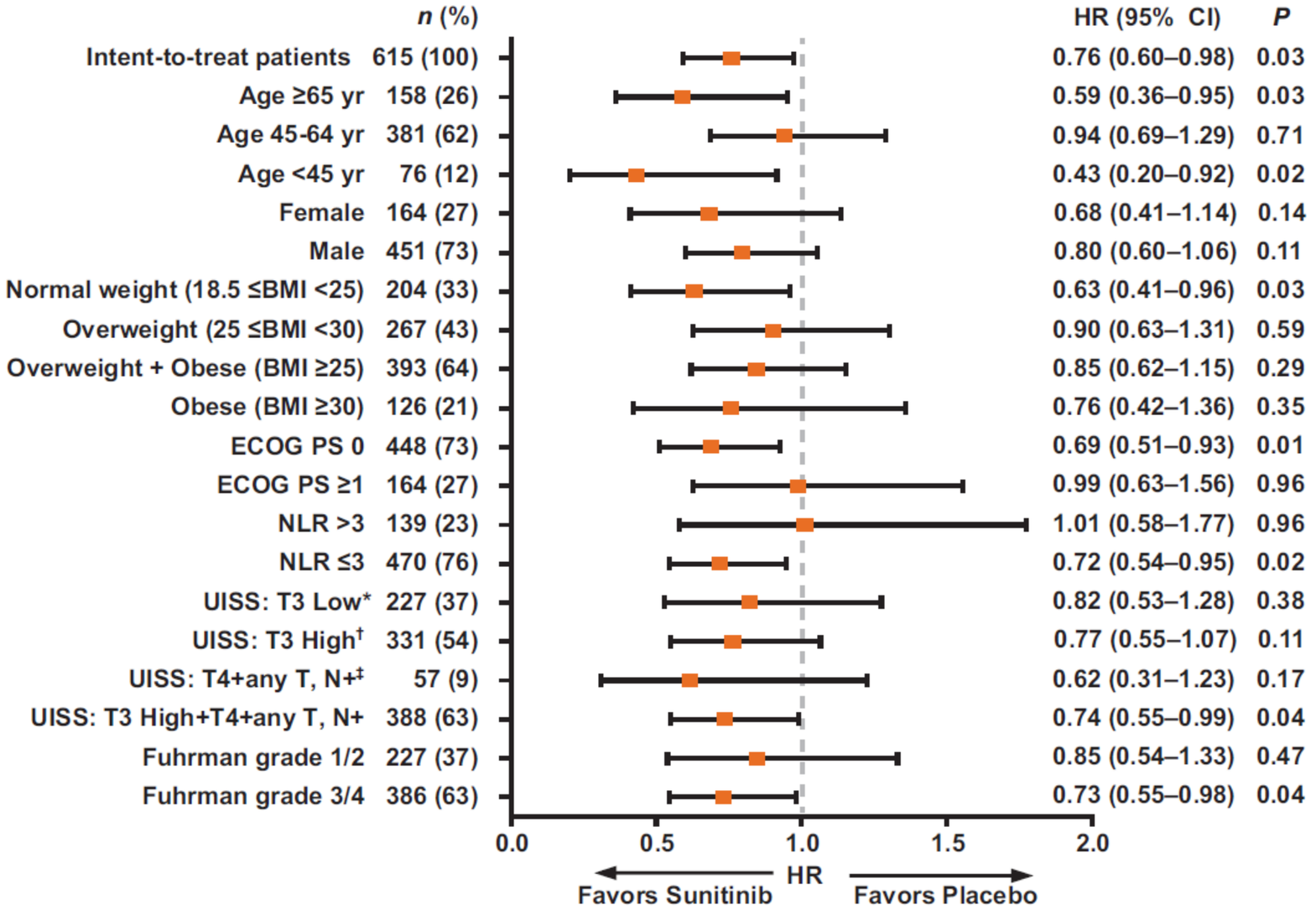
S-TRAC Phase III trial: DFS benefit with Adjuvant sunitinib



- Sunitinib 50 mg/day or placebo 4-weeks-on, 2-weeks-off x 1 year
- Clear-cell RCC
- T3 or T4, any T stage with nodal involvement
- Any Fuhrman grade
- ECOG PS 0-2 before nephrectomy
- No macroscopic residual disease
- within 3–12 wk after nephrectomy

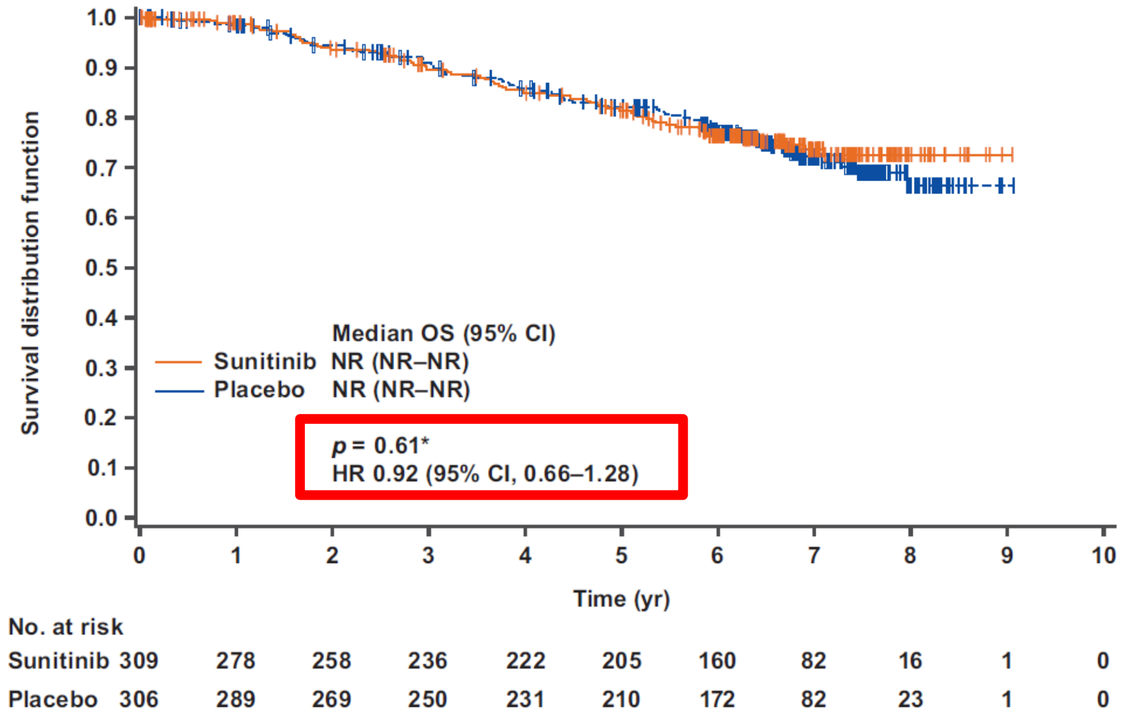
Ravaud A, NEJM 2016; Motzer R et al, Eur Urol 2017

S-TRAC Phase III trial: DFS sub-analyses



Ravaud A, NEJM 2016; Motzer R et al, Eur Urol 2017

S-TRAC Phase III trial: Adjuvant sunitinib provided no OS benefit & was associated with toxicities

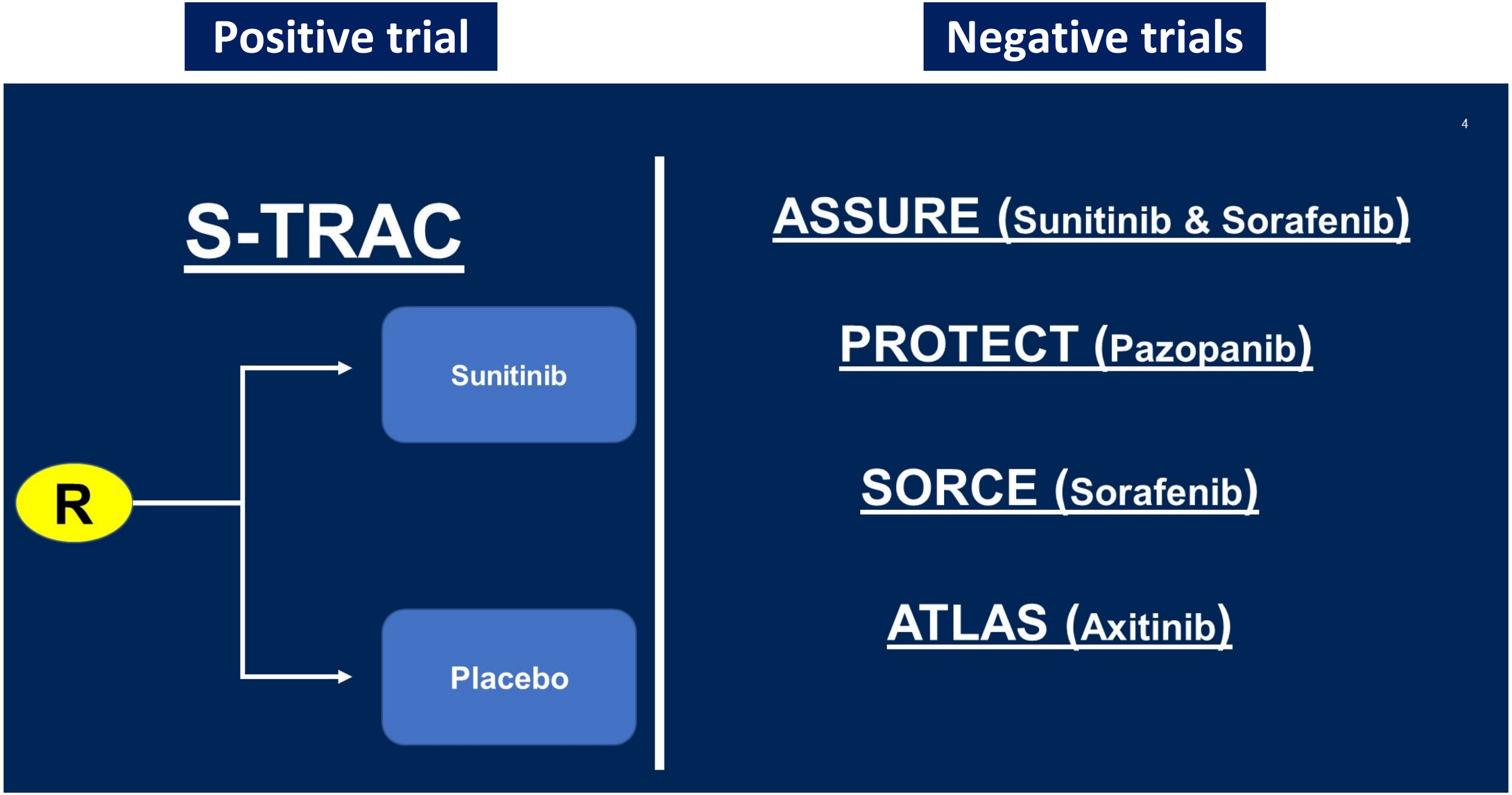


Event	Sunitinib (N=306)			Placebo (N=304)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	305 (99.7)	148 (48.4)	37 (12.1)	269 (88.5)	48 (15.8)	11 (3.6)
Diarrhea	174 (56.9)	12 (3.9)	0	65 (21.4)	1 (0.3)	0
Palmar–plantar erythrodysesthesia	154 (50.3)	46 (15.0)	3 (1.0)	31 (10.2)	1 (0.3)	0
Hypertension	113 (36.9)	24 (7.8)	0	36 (11.8)	3 (1.0)	1 (0.3)
Fatigue	112 (36.6)	13 (4.2)	2 (0.7)	74 (24.3)	4 (1.3)	0
Nausea	105 (34.3)	6 (2.0)	0	42 (13.8)	0	0
Dysgeusia	103 (33.7)	0	0	18 (5.9)	0	0
Mucosal inflammation	103 (33.7)	14 (4.6)	0	25 (8.2)	0	0
Dyspepsia	82 (26.8)	4 (1.3)	0	19 (6.3)	0	0
Stomatitis	81 (26.5)	5 (1.6)	2 (0.7)	13 (4.3)	0	0
Neutropenia	72 (23.5)	23 (7.5)	3 (1.0)	2 (0.7)	0	0
Asthenia	69 (22.5)	11 (3.6)	0	37 (12.2)	2 (0.7)	1 (0.3)
Hair-color change	68 (22.2)	0	0	7 (2.3)	0	0
Thrombocytopenia	64 (20.9)	15 (4.9)	4 (1.3)	5 (1.6)	1 (0.3)	0
Decreased appetite	59 (19.3)	2 (0.7)	0	16 (5.3)	0	0
Rash	59 (19.3)	2 (0.7)	0	29 (9.5)	0	0
Vomiting	58 (19.0)	7 (2.3)	0	20 (6.6)	0	0
Headache	57 (18.6)	2 (0.7)	0	36 (11.8)	0	0
Hypothyroidism	56 (18.3)	0	0	4 (1.3)	0	0
Epistaxis	55 (18.0)	0	0	9 (3.0)	0	0

Treatment discontinuations owing to AEs occurred in 86 patients (28.1%) with sunitinib and 17 (5.6%) with placebo

Ravaud A, NEJM 2016; Motzer R et al, Eur Urol 2017

Trials evaluating adjuvant VEGF inhibitors



Potential reasons for discordant results with adjuvant VEGF inhibitors

Trial identifier	Therapeutic agent	Inclusion criteria (tumour stage and grade)	Histology	Results for primary end point
ASSURE NCT00326898	Sunitinib 50 mg daily (amended to 37.5 mg daily with dose escalation) for 4 weeks on and 2 weeks off for 9 cycles (1 year) Sorafenib 400 mg twice daily (amended to 400 mg daily with dose escalation) for 54 weeks	pT1b N0 (G3–4), pT2–4 N0, pT(any) N1	All subtypes (except duct–Bellini subtype)	DFS, sunitinib versus placebo: HR 1.02, 95% CI 0.85–1.23; *P*=0.80 DFS, sorafenib versus placebo: HR 0.97, 95% CI 0.80–1.17; *P*=0.71
S-TRAC NCT00375674	Sunitinib 50 mg daily (4 weeks on and 2 weeks off)	pT3 N0 (G2–4), pT4 N0, pT(any) N1	ccRCC	DFS, sunitinib versus placebo: HR 0.76, 95% CI 0.59–0.98; *P*=0.03
PROTECT NCT04321148	Pazopanib 800 mg daily (amended to 600 mg daily with dose escalation)	pT2–4 N0 (G3–4), pT3–4 N0, pT(any) N1	ccRCC	DFS, pazopanib 600 mg starting dose versus placebo: HR 0.86, 95% CI 0.70–1.06; *P*=0.165
ATLAS NCT01599754	Axitinib 5 mg twice daily for 3 years	pT2–4 N0, pT(any) N1	>50% ccRCC	DFS, axitinib versus placebo: HR 0.87, 95% CI 0.660–1.147; *P*=0.321
SORCE NCT004922	Sorafenib 400 mg twice daily (amended to 400 mg daily with dose escalation) for 1 or 3 years	pT1a N0 (G4 only) pT1b N0 (G3–4), pT2–4 N0, pT1b–pT4 N1	All subtypes	DFS, sorafenib versus placebo: HR 1.01, 95% CI 0.83–1.23; *P*=0.99

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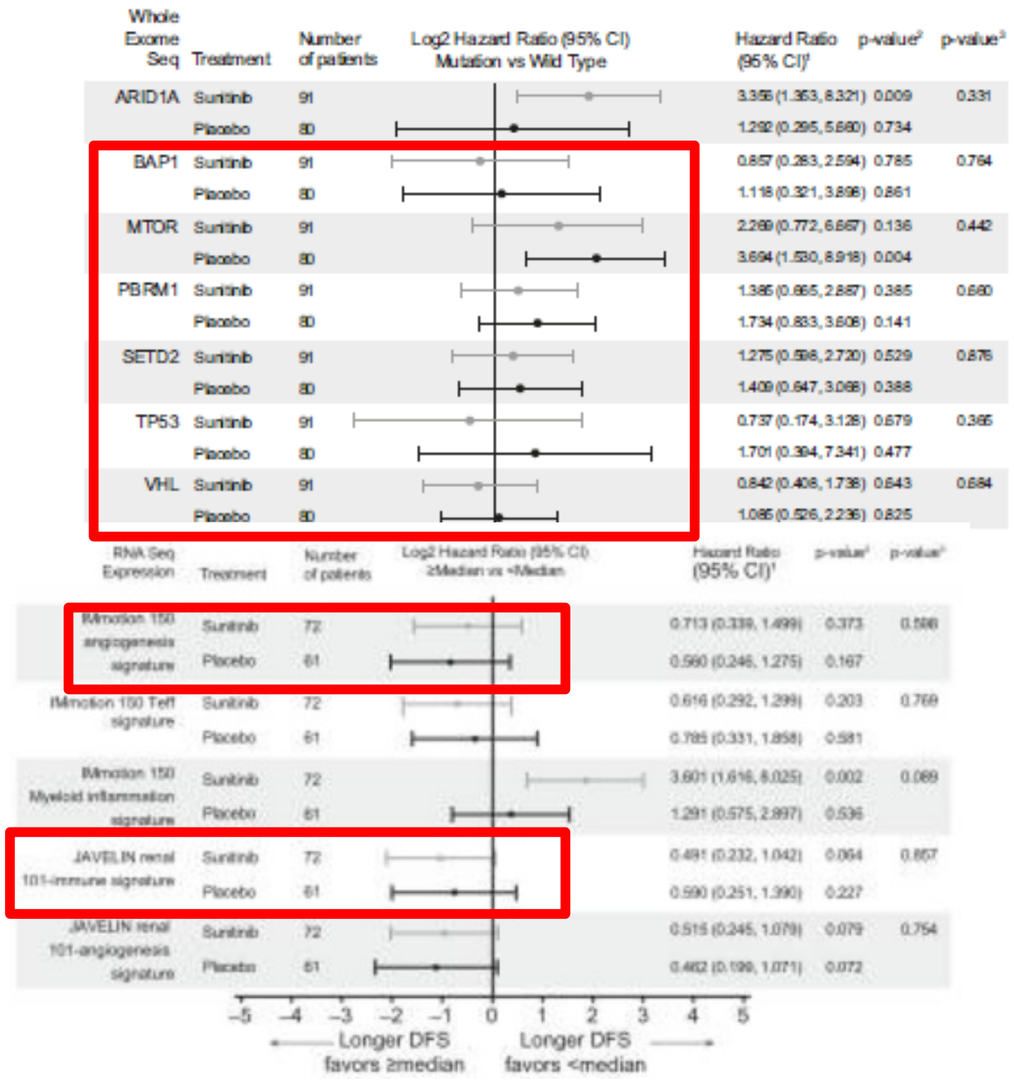
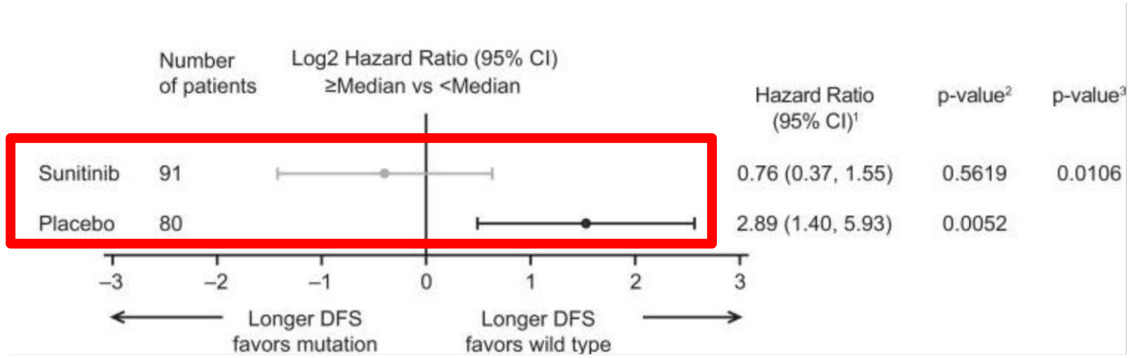
Molecular characterization of renal cell carcinoma tumors from a phase III anti-angiogenic adjuvant therapy trial





Comprehensive genomic and transcriptomic analysis of tumors from **171/615 patients from the S-TRAC trial**

DFS was not significantly influenced by mutations in *VHL*, *PBRM1*, *SETD2* and *BAP1*.

High TMB = worse survival, but adjuvant sunitinib largely abrogated this prognostic effect, suggesting that high TMB may confer a clinical benefit from adjuvant sunitinib.

Low expression of **STRAC11 GES associated with better OS with sunitinib** (STRACII enriched for regulation of the stroma (TDO2, STEAP1), Treg cells (SLC16A1, PRKAB1) and myeloid cells (APOBEC3A, MERTK, SNX29).

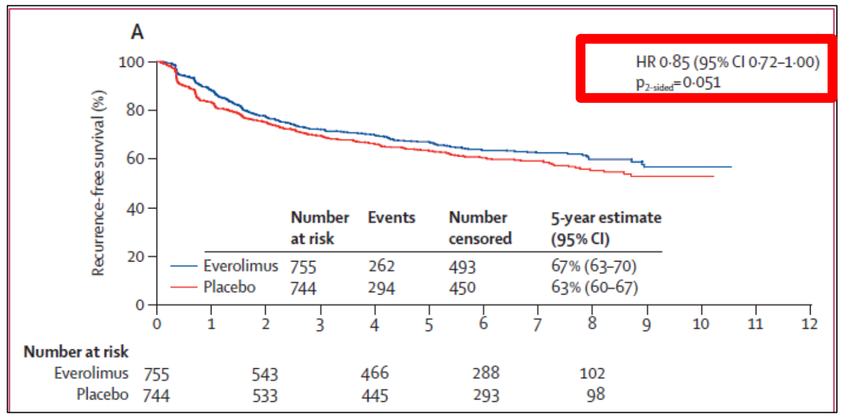
Angiogenic signatures derived from metastatic RCC trials IMmotion 150 GES and JAVELIN Renal 101 GES were applied to S-TRAC:

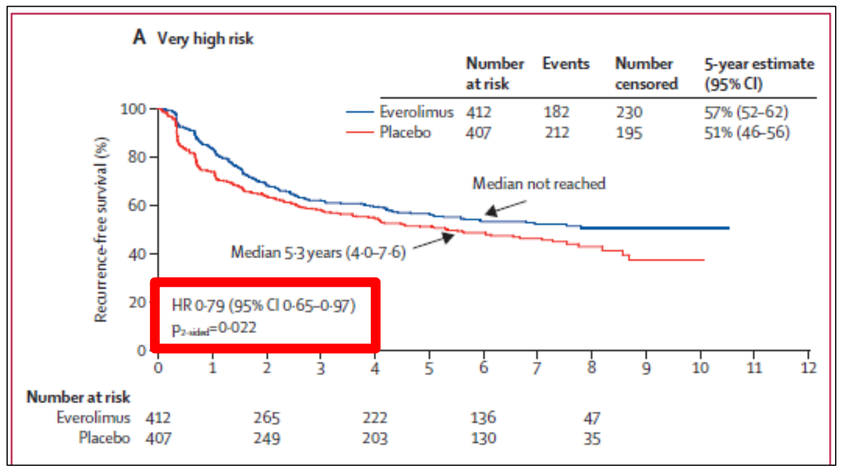
- IMmotion 150 GES appeared to be **prognostic for better OS**
- JAVELIN Renal 101 GES appeared **predictive** of better OS with adjuvant sunitinib.

Motzer RJ, et al. Nat Commun 2022; Oct 10;13(1):5959.

EVEREST Phase III trial: Adjuvant Everolimus (mTOR inhibitor)

No Overall RFS benefit (≥pT1b high grade or N+), but potential benefit in very high-risk subset



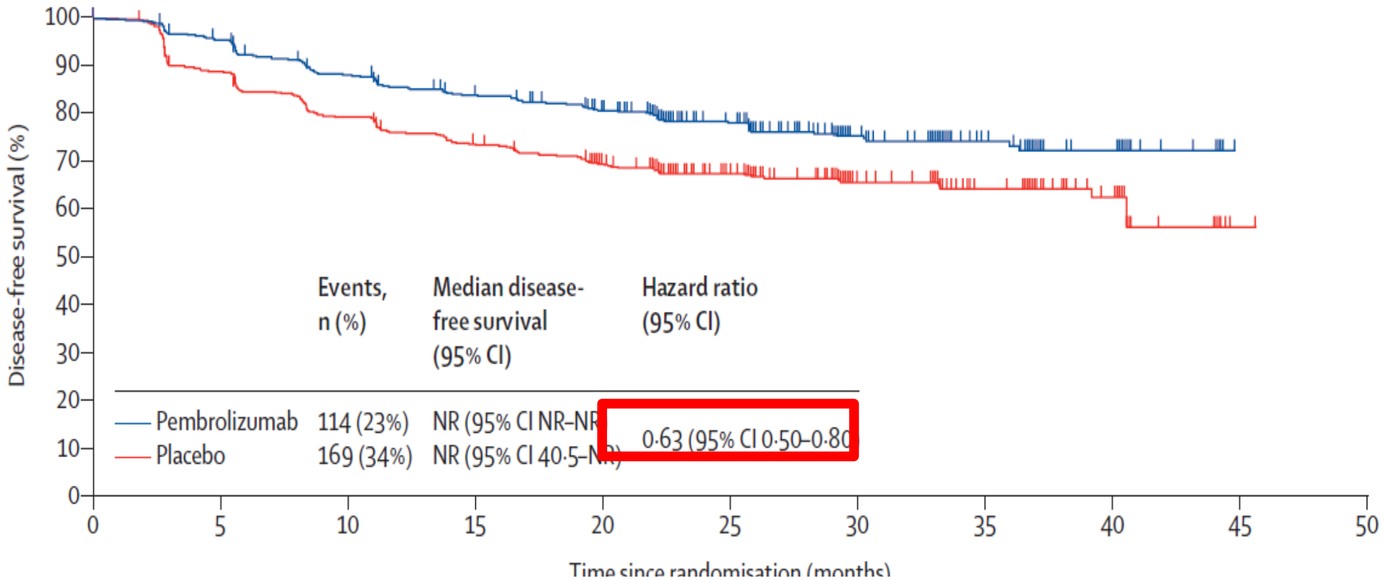


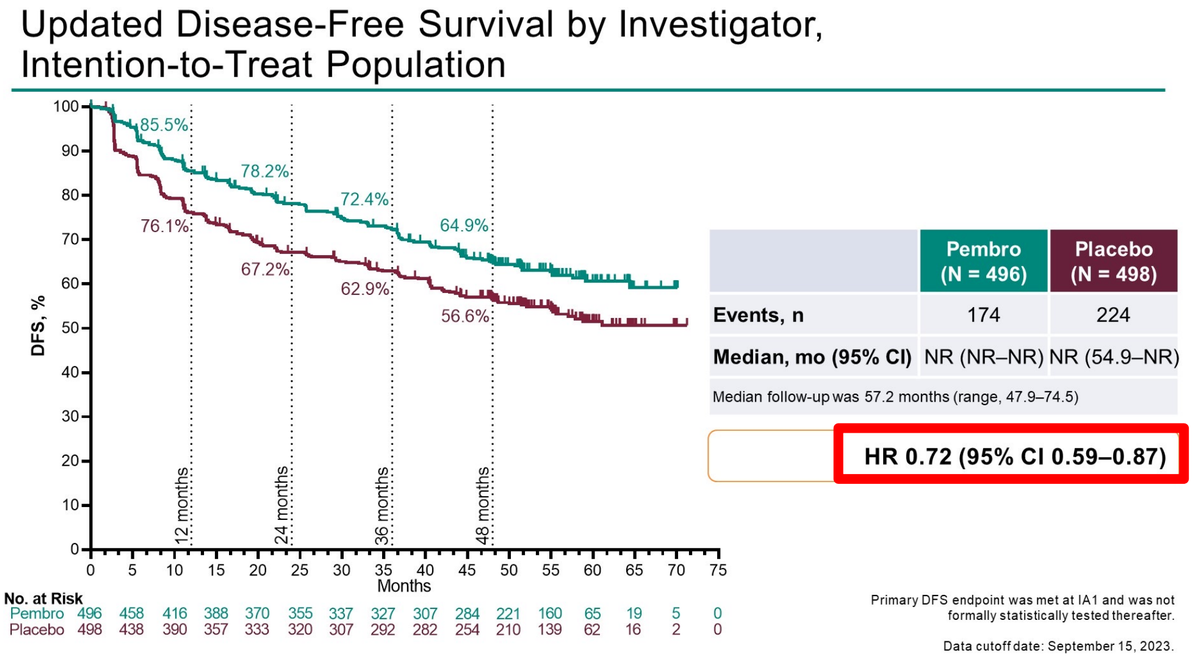
	Everolimus (N=755)	Placebo (N=744)
Median time on treatment, months	9.3	12.6
Dose reductions	37%	7%
Discontinuation, not due to progression or death %	47%	17%

- Postoperative everolimus (1 year) **did not improve recurrence-free survival** vs. placebo among patients with renal cell carcinoma at high risk of recurrence after nephrectomy.
- There may be a **benefit in a very-high risk subgroup** with adjuvant everolimus (unplanned analysis).
- **Grade 3–4 toxicities** occurred in 46% of patients receiving everolimus and 37% discontinued early due to adverse events, which may have compromised outcomes.

Ryan C, et al. Lancet 2023 Sep 23;402(10407):1043-1051.

Adjuvant pembrolizumab (KEYNOTE564): Improved DFS





	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.

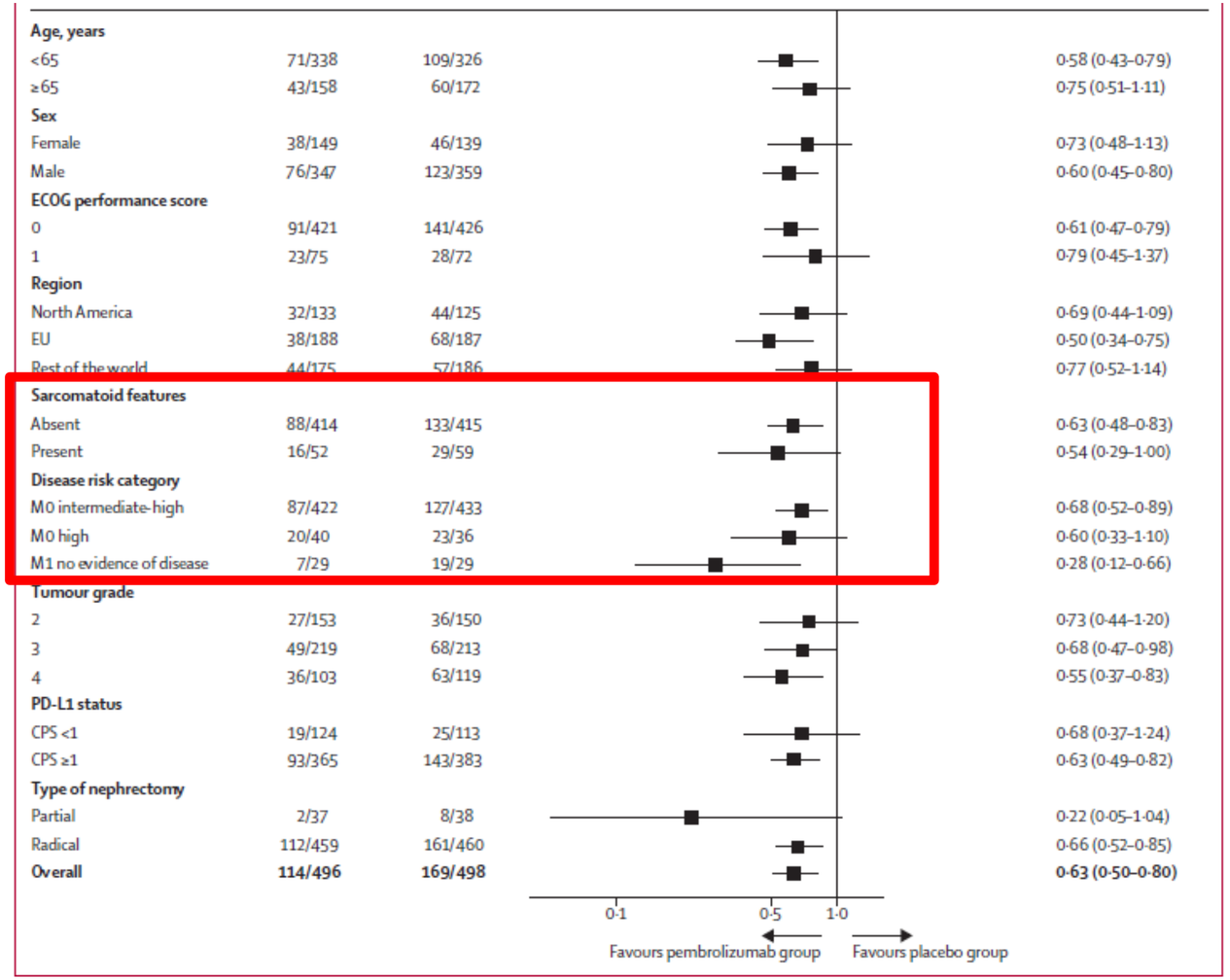
Data cutoff date: September 15, 2023.

- 1 year of pembro vs. placebo
- RCC with clear cell component +/- sarcomatoid
- pT2 grade 4 or sarcomatoid differentiation
- pT3-T4, any grade or N+
- M1 with no evidence of disease after complete resection of oligometastases synchronously or within 1 year of nephrectomy

Powles T,,…Choueiri TK. Lancet Oncol 2022; Choueiri TK, et al. GU ASCO 2024

Adjuvant pembrolizumab (KEYNOTE564)

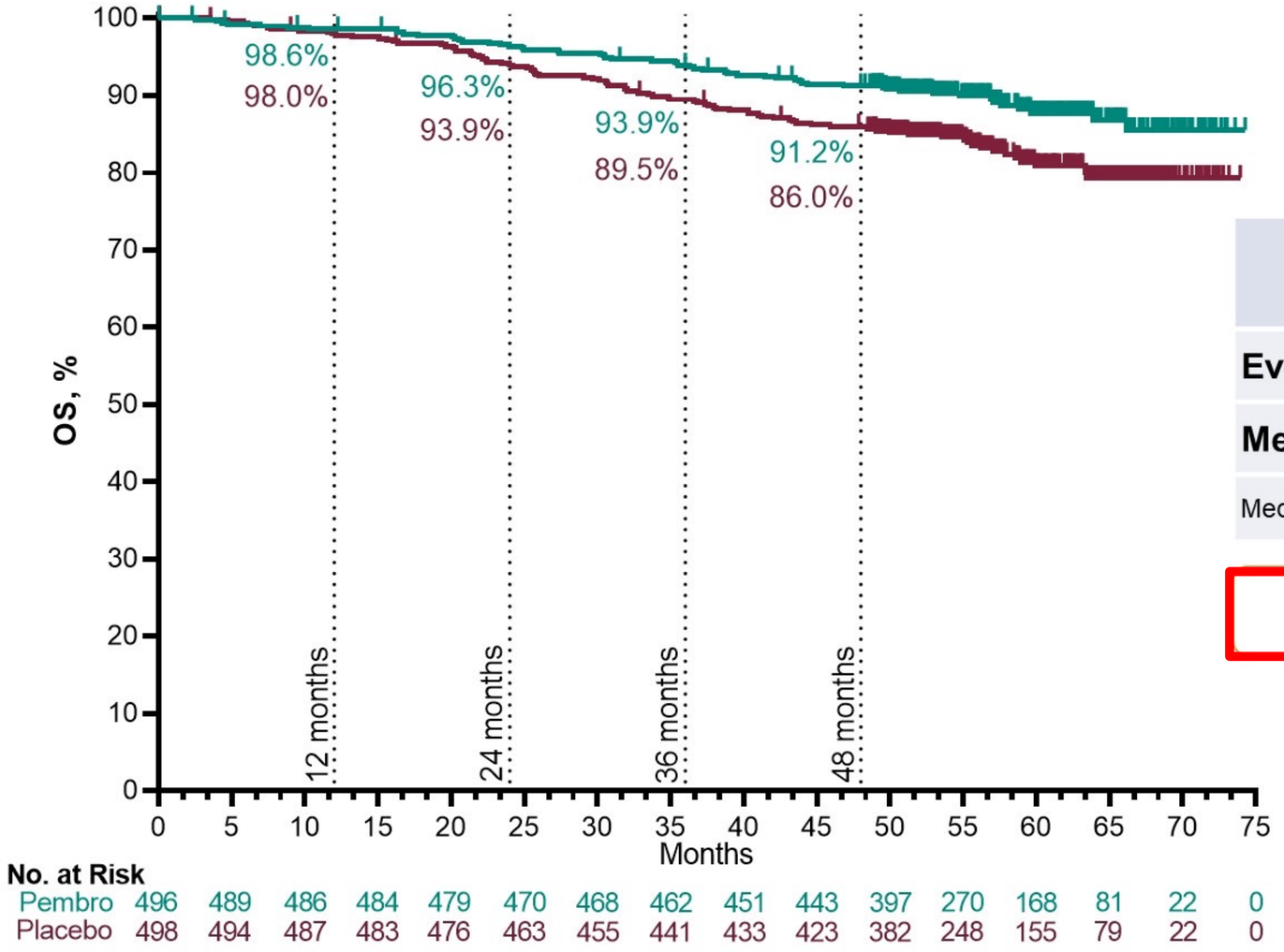
DFS benefits in subgroups



Powles T,,…Choueiri TK. Lancet Oncol 2022

Adjuvant pembrolizumab (KEYNOTE564): OS improvement seen

Overall Survival, Intention-to-Treat Population



	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)		

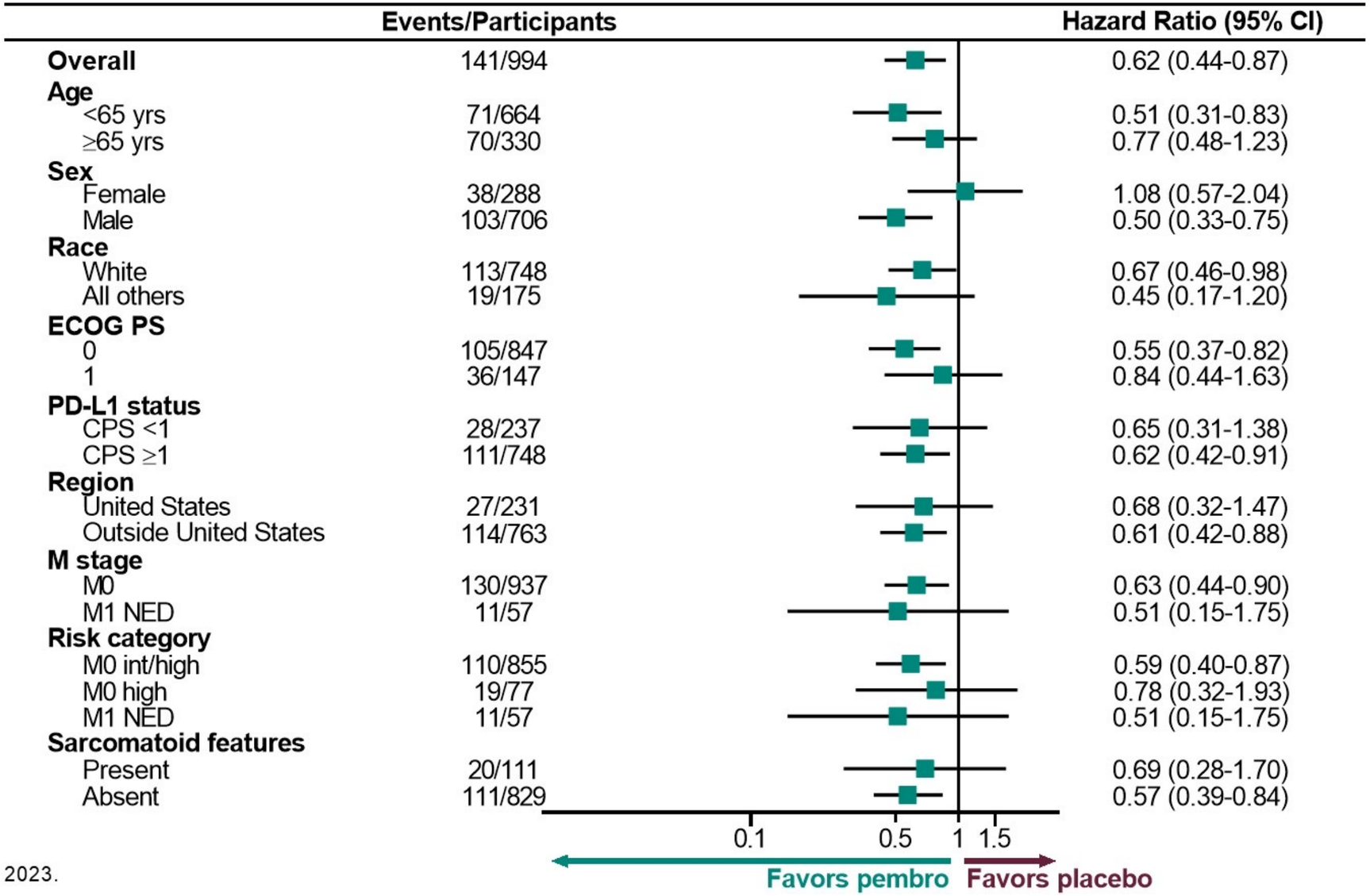
HR 0.62 (95% CI 0.44–0.87); *P* =.002*

* **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.

Choueiri TK, et al. GU ASCO 2024

Adjuvant pembrolizumab (KEYNOTE564): OS improvement across subgroups



Data cutoff date: September 15, 2023.

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Adjuvant pembrolizumab (KEYNOTE564): subsequent therapy

	Participants with Documented Recurrence	
	Pembrolizumab (N = 161)	Placebo (N = 210)
Received any subsequent therapy[a,b]	128/161 (79.5%)	171/210 (81.4%)
Received systemic anticancer drug therapy	102/128 (79.7%)	145/171 (84.8%)
Anti–PD-(L)1 therapy[c]	42/102 (41.2%)	101/145 (69.7%)
VEGF/VEGFR inhibitor[d]	94/102 (92.2%)	123/145 (84.8%)
Other[e]	32/102 (31.4%)	60/145 (41.4%)
Received radiation therapy	31/128 (24.2%)	33/171 (19.3%)
Received surgery	35/128 (27.3%)	50/171 (29.2%)
No subsequent therapy	28/161 (17.4%)	28/210 (13.3%)
No subsequent therapy data available	5/161 (3.1%)	11/210 (5.2%)

[a]An additional 4 and 1 pts respectively in the pembro and placebo arms who are not included in the figure received subsequent therapy without documented recurrence. [b]Pts could have multiple subsequent anticancer therapies for RCC; each pt is counted once in each applicable category. [c]Atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab. [d]Axitinib, bevacizumab, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib, tivozanib. [e]Included but was not limited to belzutifan, everolimus, and ipilimumab.
Data cutoff date: September 15, 2023.

Powles T,…Choueiri TK. Lancet Oncol 2022
Choueiri TK, et al. GU ASCO 2024

Adjuvant pembrolizumab (KEYNOTE564): Toxicities

Summary of Updated Safety Findings, As-Treated Population

	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%)

[a]AEs were graded per the NCI CTCAE v4.0 and reported from randomization to 30 days (90 days for serious AEs) after study therapy discontinuation. [b]Based on a list of preferred terms intended to capture known risks of pembro and were considered regardless of attribution to study treatment by the investigator.
Data cutoff date: September 15, 2023.

Powles T,…Choueiri TK. Lancet Oncol 2022
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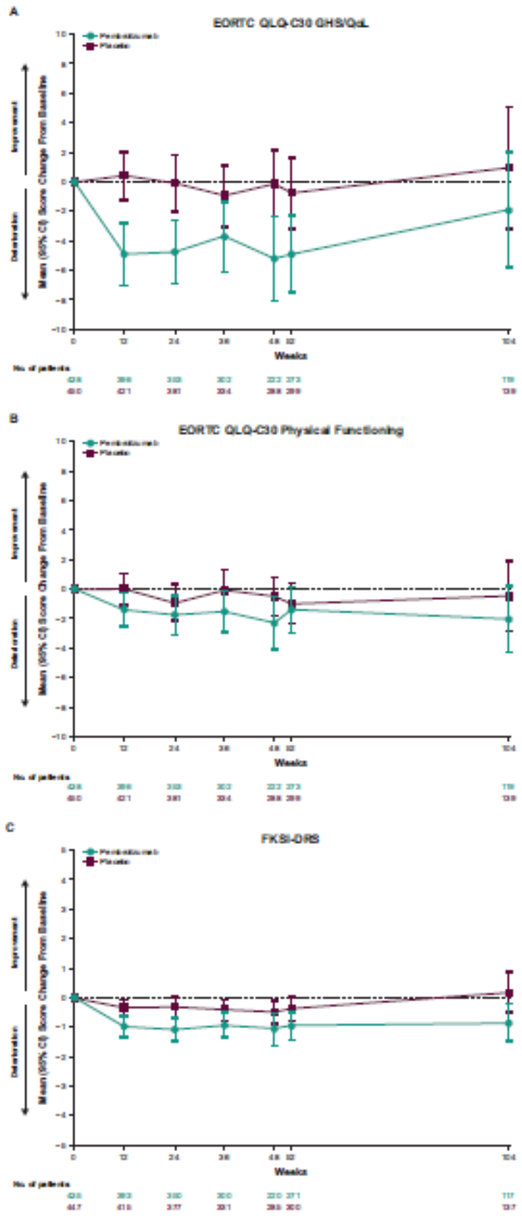
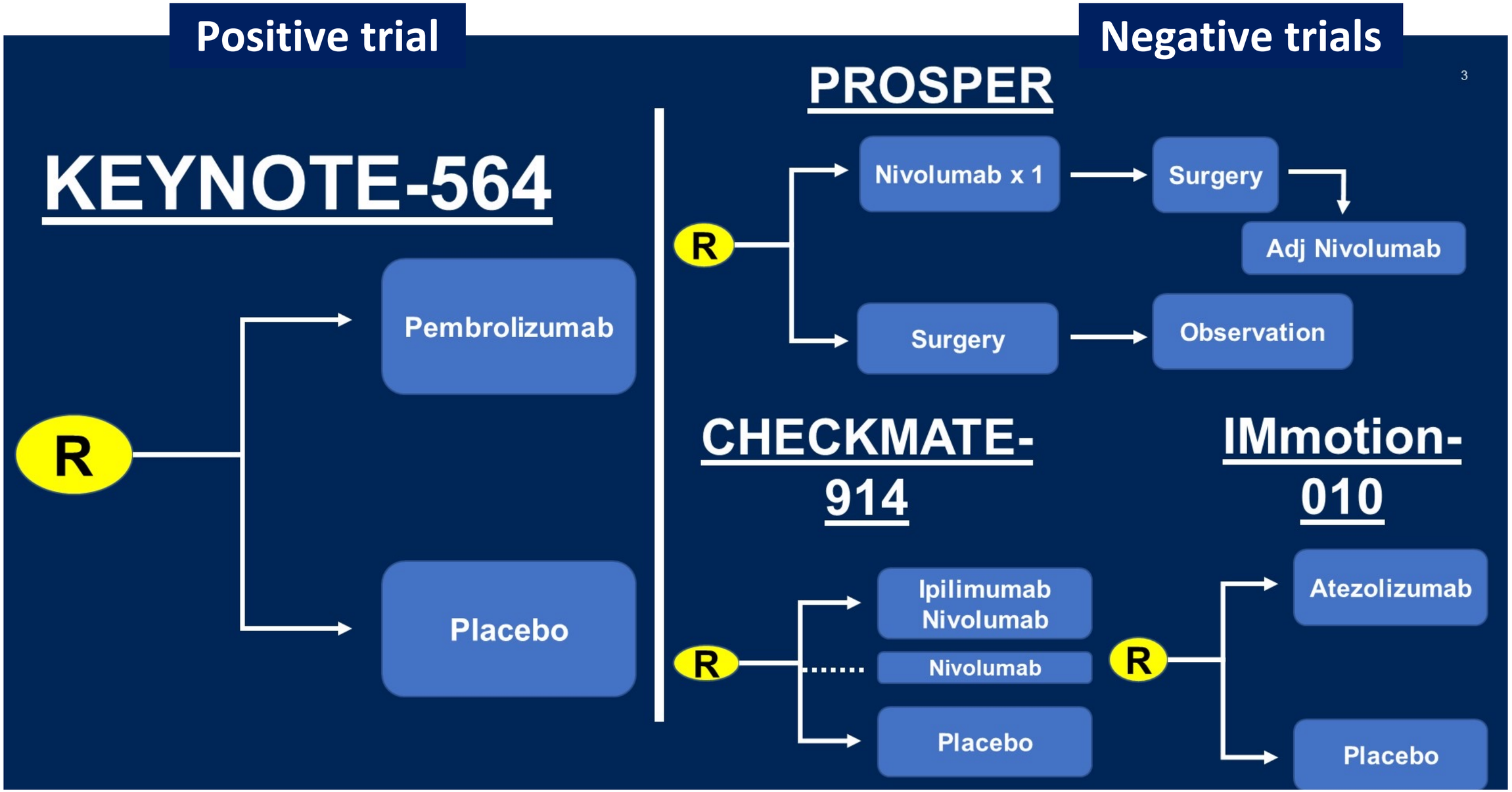
Adjuvant pembrolizumab (KEYNOTE564): PRO



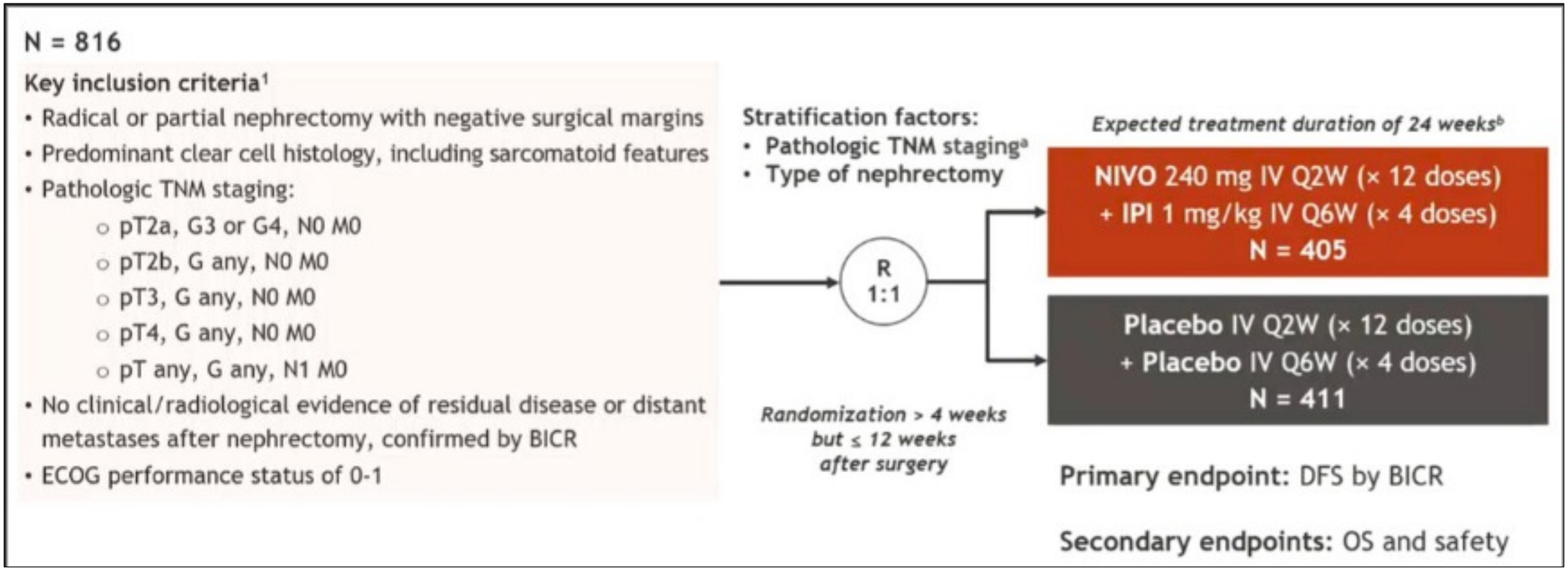
- **No meaningful differences** were observed between the pembrolizumab and placebo groups in the other EORTC QLQ-C30 functional or symptom scales or in the EQ-5D VAS.
- **Mean change from baseline remained stable** in the EORTC QLQ-C30 GHS/QoL and physical functioning scales and in the FKSI-DRS through week 104 for both the pembrolizumab and placebo groups.
- Although patients in the placebo group did not receive active treatment, PRO outcomes were comparable between groups.
- Therefore, **pembrolizumab did not have a negative impact on HRQoL.**

Choueiri TK, et al. Oncologist 2023

Trials evaluating adjuvant immune checkpoint inhibitors

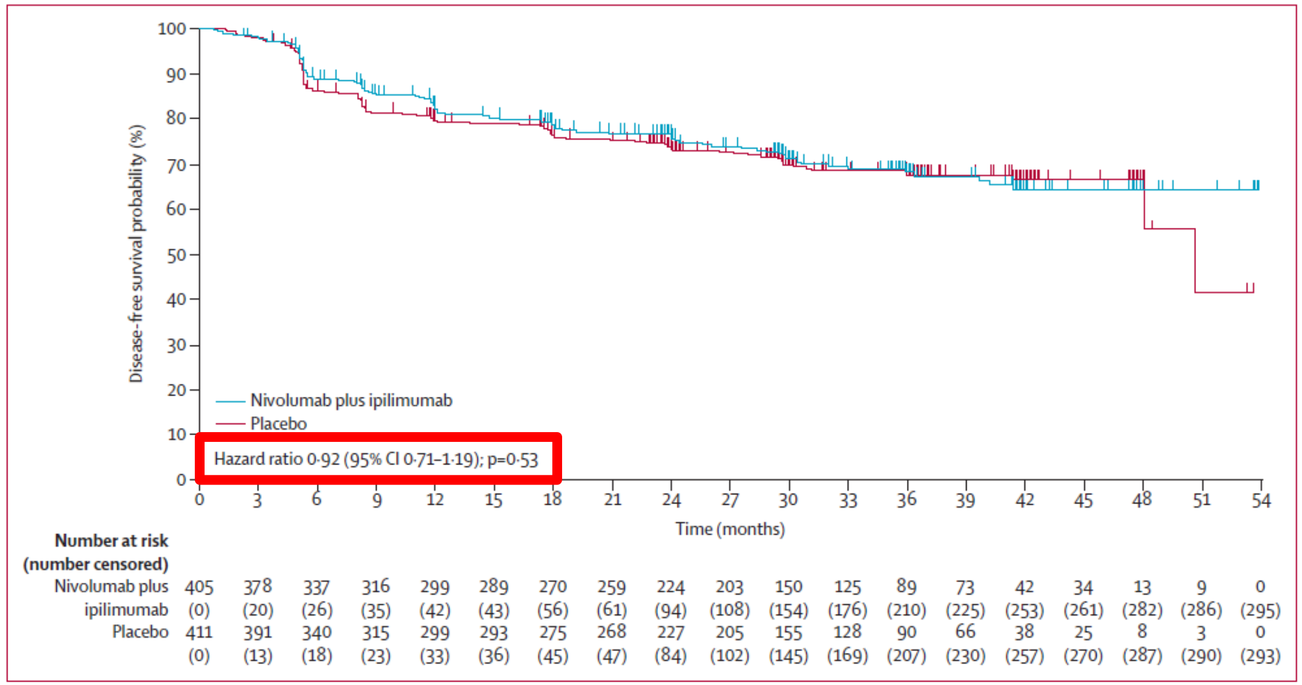


CHECKMATE-914: Adjuvant IPI-NIVO



Motzer RJ, et al. Lancet 2023. Mar 11;401(10379):821-832.

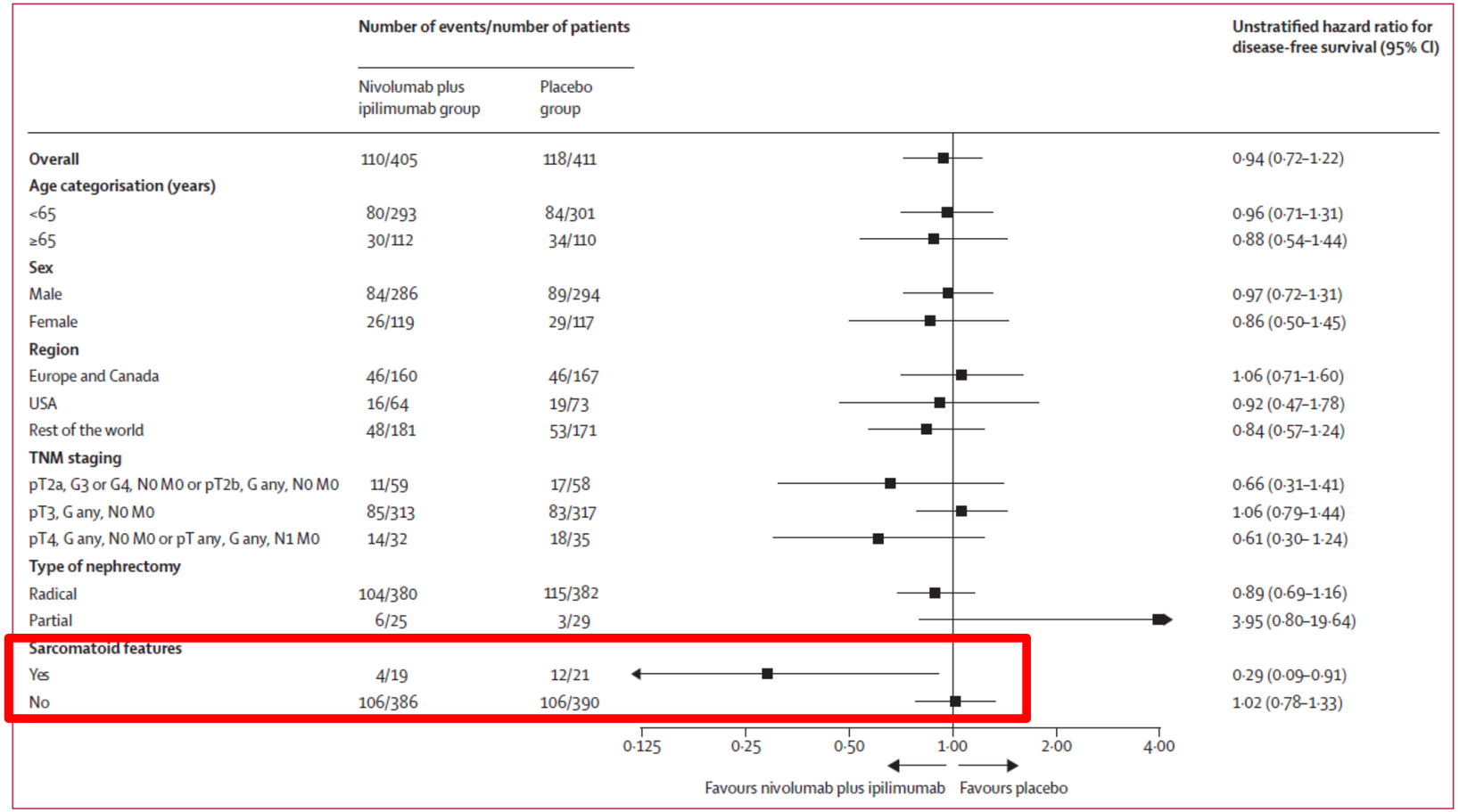
CHECKMATE-914: Adjuvant IPI-NIVO



Adjuvant therapy with nivolumab plus ipilimumab **did not improve disease-free survival** versus placebo in patients with localized renal cell carcinoma at high risk of recurrence after nephrectomy.

Motzer RJ, et al. Lancet 2023. Mar 11;401(10379):821-832.

CHECKMATE-914: Adjuvant IPI-NIVO
Sub-analyses



Motzer RJ, et al. Lancet 2023. Mar 11;401(10379):821-832.

CHECKMATE-914: Adjuvant IPI-NIVO

Did toxicities compromise efficacy?

	Nivolumab (in nivolumab plus ipilimumab group; n=404)	Ipilimumab (in nivolumab plus ipilimumab group; n=403)	Nivolumab placebo (in placebo group; n=407)	Ipilimumab placebo (in placebo group; n=406)
Median number of doses received (range; IQR)*	12 (1–12; 6–12)	4 (1–4; 2–4)†	12 (1–12; 12–12)	4 (1–4; 4–4)†
Last cycle received before treatment period ended				
1	17	51	5	8
2	21	..	2	..
3	14	..	2	..
4	22	50	4	12
5	16	..	2	..
6	12	..	5	..
7	13	36	6	14
8	13	..	3	..
9	10	..	6	..
10	12	266	5	372
11	24	..	6	..
12‡	230	..	361	..
Patients with at least one dose delay§	141 (35%)	136 (34%)	110 (27%)	104 (26%)
Relative dose intensity¶				
≥110%	0	0	..	..
90% to <110%	332 (82%)	346 (86%)	..	..
70% to <90%	63 (16%)	52 (13%)	..	..
50% to <70%	7 (2%)	4 (1%)	..	..
<50%	2 (<1%)	1 (<1)	..	..

- Treatment-related adverse events of any grade led to **discontinuation of nivolumab plus ipilimumab in 29%** of IPI-NIVO patients.
- In the nivolumab plus ipilimumab group, 57% of patients completed all cycles of nivolumab and 66% completed all cycles of ipilimumab
- 23% of patients treated with nivolumab plus ipilimumab received corticosteroids (≥40 mg /d prednisone or equivalent).

Motzer RJ, et al. Lancet 2023. Mar 11;401(10379):821-832.

Study design (Part B)

N = 825

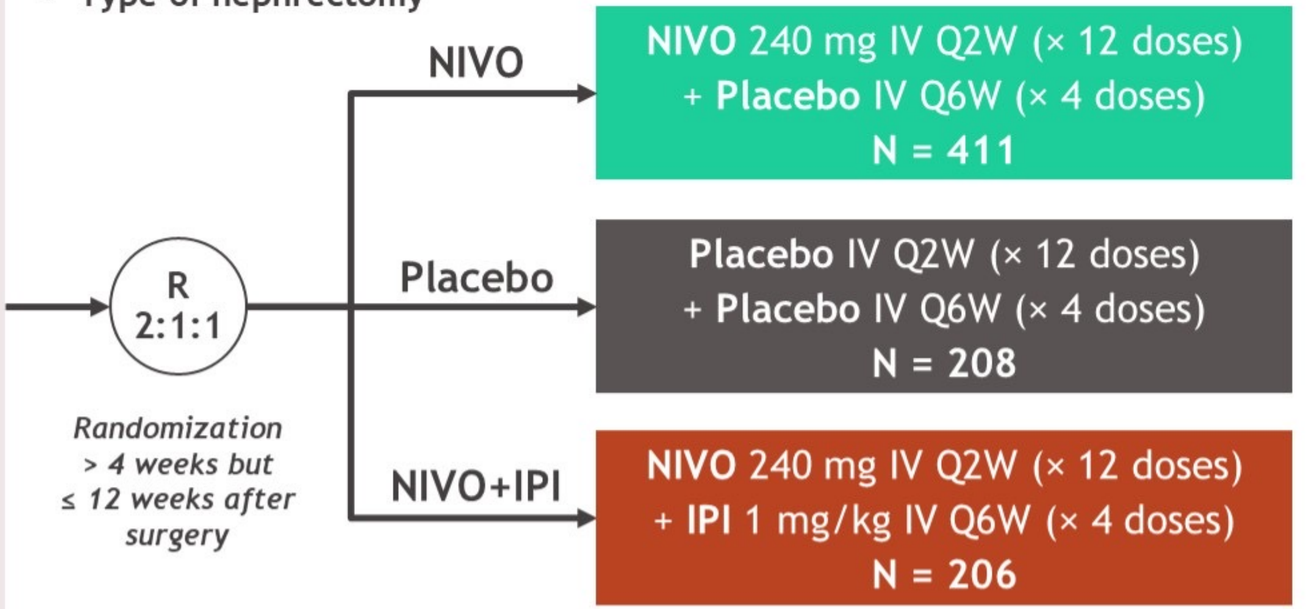
Key inclusion criteria[1]

- Radical or partial nephrectomy with negative surgical margins
- Predominant clear cell histology, including sarcomatoid features
- Pathologic TNM staging:
  - pT2a, G3 or G4, N0 M0
  - pT2b, G any, N0 M0
  - pT3, G any, N0 M0
  - pT4, G any, N0 M0
  - pT any, G any, N1 M0
- No clinical/radiological evidence of residual disease or distant metastases after nephrectomy, confirmed by BICR
- ECOG performance status of 0-1

Median (range) study follow-up, 27.0 (18.0-42.4) months

Stratification factors:

- **Pathologic TNM staging**[a]
- **Type of nephrectomy**



Primary endpoint: DFS per BICR for NIVO vs placebo

Secondary endpoints: DFS per BICR for NIVO+IPI vs NIVO,[c] OS for NIVO vs placebo (and NIVO+IPI vs NIVO[c]), and safety

Key exploratory endpoint: HRQoL

[a]Stratification was based on the following TNM staging groups: pT2a, G3 or G4, N0 M0 or pT2b, G any, N0 M0 vs pT3, G any, N0 M0 vs pT4, G any, N0 M0 or pT any, G any, N1 M0. [b]Treatment could be extended up to 36 weeks to accommodate dose delays. [c]Contribution of components analysis.

1. ClinicalTrials.gov. Accessed December 11, 2023. https://clinicaltrials.gov/ct2/show/NCT03138512.

Motzer RJ, et al. GU ASCO 2024.

CHECKMATE-914: Part B

Select baseline characteristics[a]

	NIVO (N = 411)	Placebo (N = 208)	NIVO+IPI (N = 206)
Median age (range), years	59 (25-86)	59 (25-80)	60 (29-81)
Male / female, n (%)	305 (74) / 106 (26)	141 (68) / 67 (32)	147 (71) / 59 (29)
Region, n (%)			
United States	59 (14)	22 (11)	30 (15)
Europe and Canada	166 (40)	89 (43)	94 (46)
Rest of the world	186 (45)	97 (47)	82 (40)
Type of nephrectomy, n (%)[b]			
Radical	383 (93)	193 (93)	193 (94)
Partial	28 (7)	15 (7)	13 (6)
Pathological TNM staging, n (%)[b]			
pT2a, G3 or G4, N0 M0 or pT2b, G any, N0 M0	47 (11)	24 (12)	24 (12)
pT3, G any, N0 M0	337 (82)	169 (81)	168 (82)
pT4, G any, N0 M0 or pT any, G any, N1 M0	27 (7)	15 (7)	14 (7)
Sarcomatoid features, n (%)	32 (8)	14 (7)	10 (5)
PD-L1 expression (tumor proportion score), n (%)[c]			
≥ 1%	47 (11)	16 (8)	22 (11)
< 1% or not evaluable	350 (85)	186 (89)	177 (86)
Not reported	14 (3)	6 (3)	7 (3)

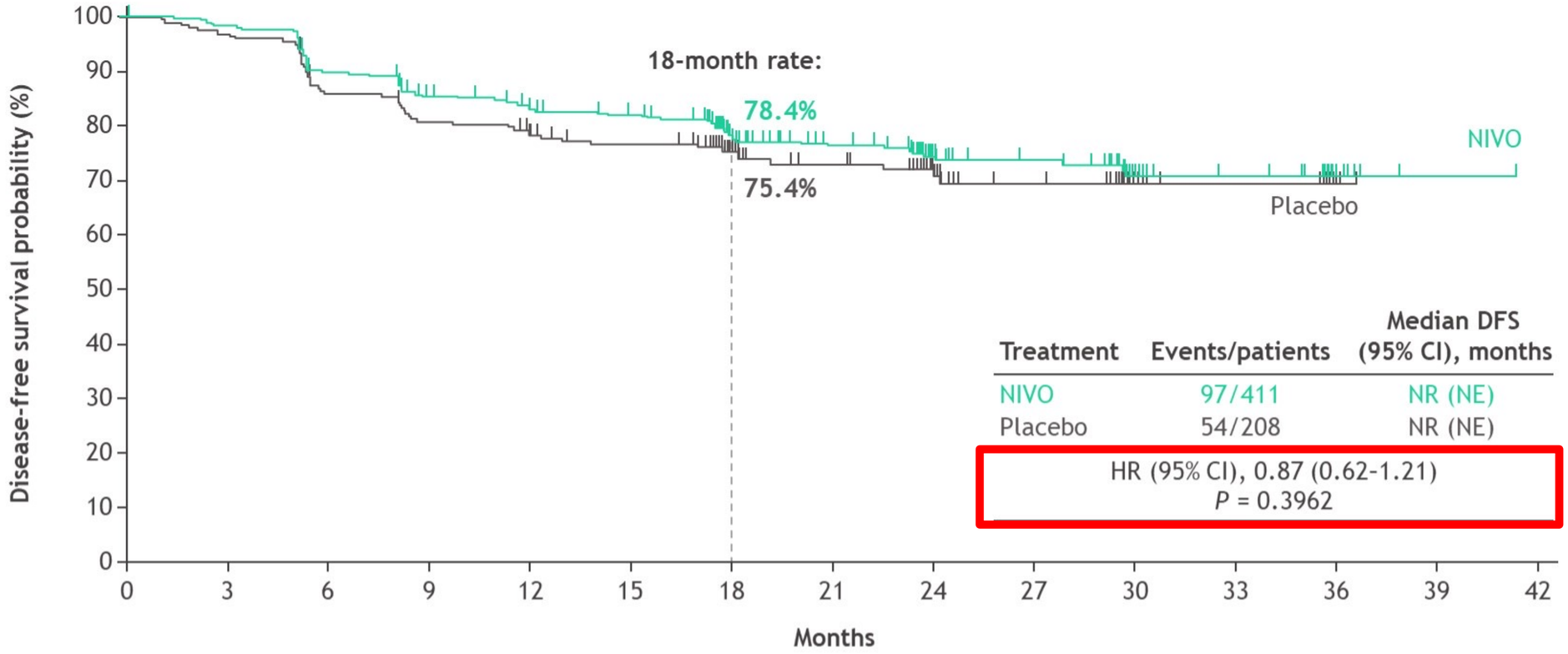
[a]In all randomized patients. [b]Per interactive response technology. [c]Per clinical database; PD-L1 testing was performed locally (Labcorp) using a validated tumor proportion score-based PD-L1 immunohistochemical assay (Dako PD-L1 IHC 28-8 pharmDx).

Motzer RJ, et al. GU ASCO 2024.

CHECKMATE-914: Part B

CheckMate 914

DFS per BICR: NIVO vs placebo (primary endpoint)



Treatment	Events/patients	Median DFS (95% CI), months
NIVO	97/411	NR (NE)
Placebo	54/208	NR (NE)

HR (95% CI), 0.87 (0.62-1.21)
P = 0.3962

No. at risk															
NIVO	411	393	356	332	317	307	232	189	110	88	32	20	7	1	0
Placebo	208	193	169	158	150	143	105	86	57	46	14	8	2	0	0

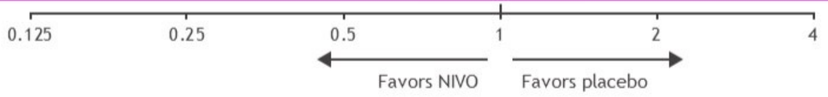
Median (range) follow-up, 27.0 (18.0-42.4) months. DFS was estimated in all randomized patients and defined as time from randomization to development of local disease recurrence, distant metastasis, or death, whichever came first. As the DFS primary endpoint was not met, no formal analysis of OS was performed (there were 19 deaths in the NIVO arm and 8 in the placebo arm).

Motzer RJ, et al. GU ASCO 2024.

CHECKMATE-914: Part B

DFS per BICR in select subgroups: NIVO vs placebo

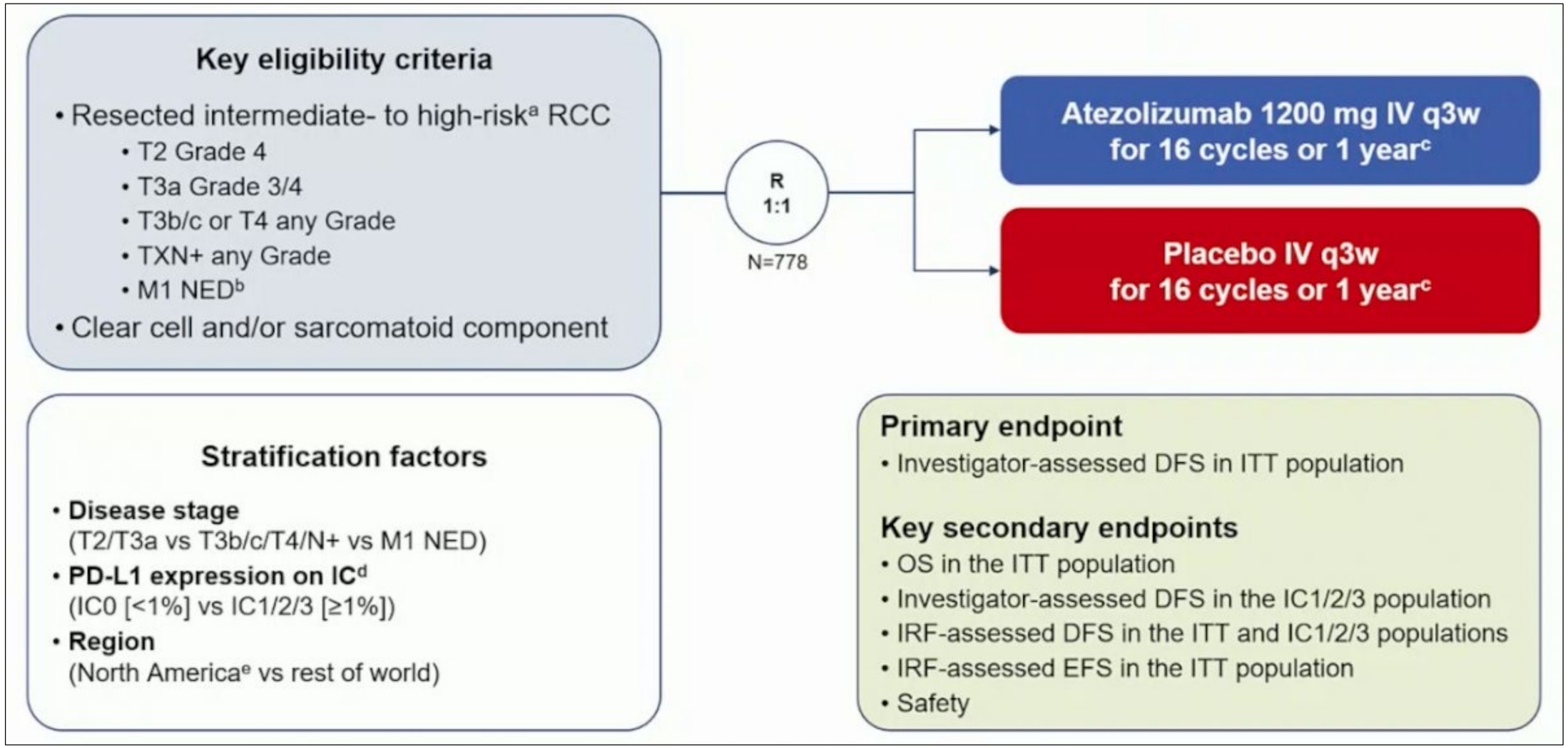
	NIVO Events/patients	Placebo Events/patients	Unstratified HR for DFS (95% CI)
Overall	97/411	54/208	0.86 (0.62-1.20)
Region			
United States	13/59	7/22	0.62 (0.25-1.57)
Europe and Canada	43/166	27/89	0.80 (0.50-1.30)
Rest of the world	41/186	20/97	1.05 (0.61-1.79)
Pathological TNM staging			
pT2a, G3 or G4, N0 M0 or pT2b, G any, N0 M0	12/45	4/22	1.54 (0.50-4.79)
pT3, G any, N0 M0	79/338	44/171	0.86 (0.60-1.25)
pT4, G any, N0 M0/pT any, G any, N1 M0	6/27	6/15	0.46 (0.15-1.43)
Type of nephrectomy			
Radical	93/384	53/194	0.85 (0.61-1.19)
Partial	4/27	1/14	1.65 (0.18-14.76)
Fuhrman grade			
G1-2	18/136	10/68	0.81 (0.37-1.75)
G2	17/127	9/64	0.87 (0.39-1.95)
G3	44/187	21/86	0.94 (0.56-1.58)
G4	35/88	23/54	0.92 (0.54-1.55)
Sarcomatoid features			
Yes	10/32	8/14	0.42 (0.17-1.07)
No	87/379	46/194	0.93 (0.65-1.32)
PD-L1 expression			
≥ 1%	13/47	8/16	0.53 (0.22-1.29)
< 1% or not evaluable	80/350	46/186	0.87 (0.61-1.25)
Hemoglobin			
< LLN	21/98	15/40	0.49 (0.25-0.95)
≥ LLN	76/313	39/167	1.01 (0.69-1.49)



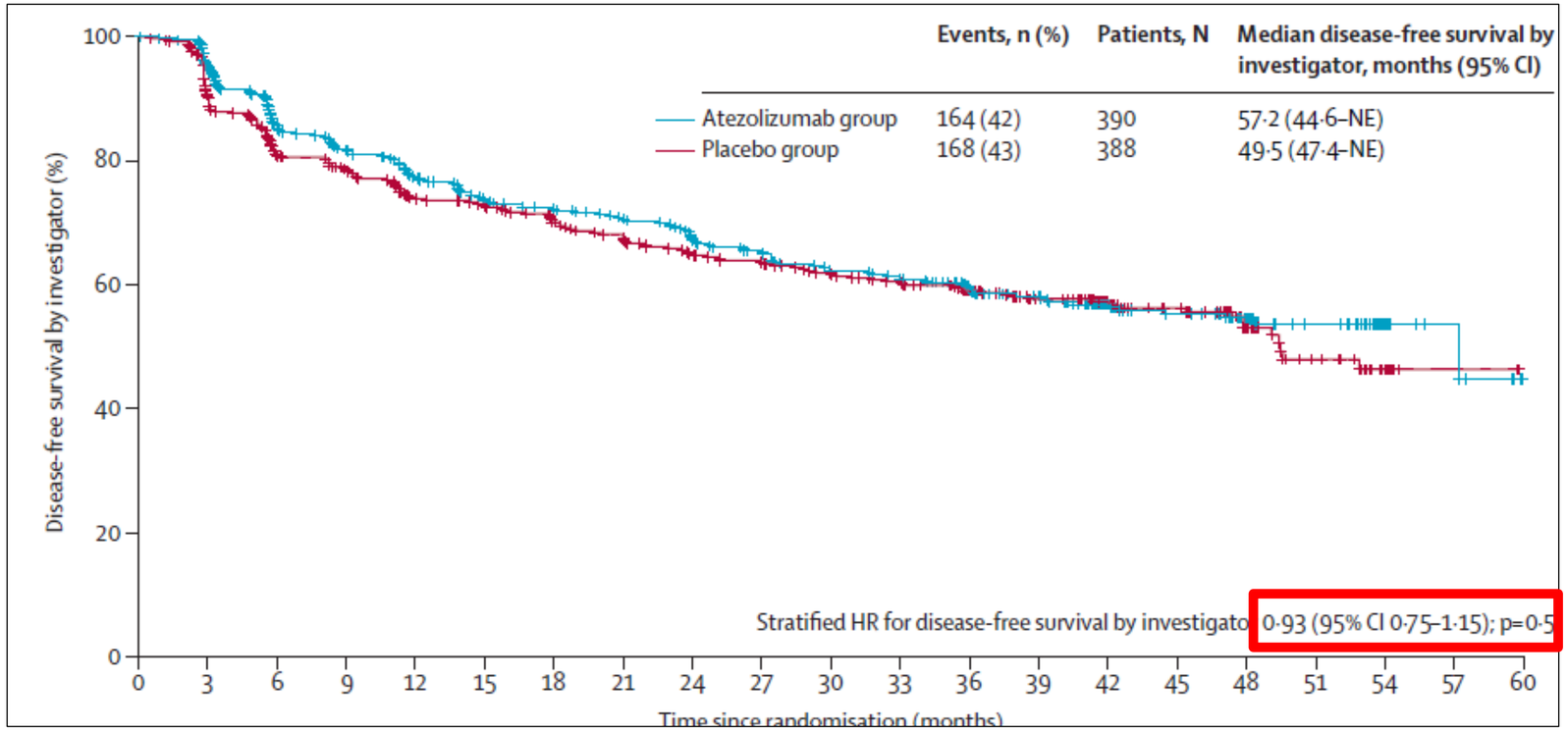
The influence of demographic and baseline clinical characteristics on DFS among all randomized patients was assessed via exploratory subgroup analyses for age, sex, region, race, ethnicity, TNM staging, type of nephrectomy, risk group, ECOG performance status, sarcomatoid features, time from diagnosis to randomization, lactate dehydrogenase level, hemoglobin, corrected calcium, alkaline phosphatase, PD-L1 status, and Fuhrman grade. The statistical analysis plan prespecified that subgroup analyses for stratification factors (TNM staging and type of nephrectomy) would only be displayed using subgroups based on case report form data.

Motzer RJ, et al. GU ASCO 2024.

IMmotion-010: adjuvant Atezolizumab



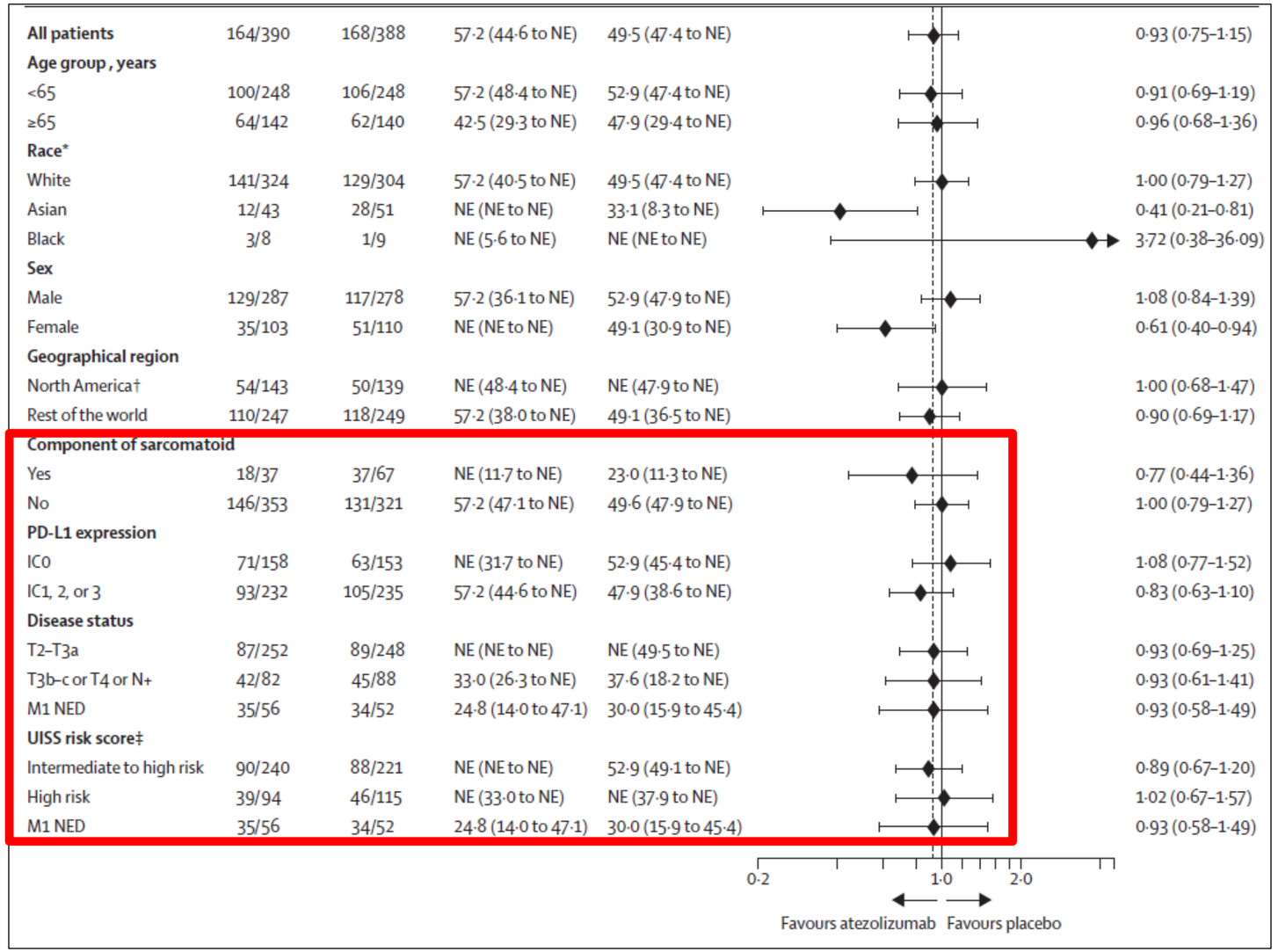
IMmotion-010: adjuvant Atezolizumab



Pal SK, et al. Lancet 2023; 2022 Oct 1;400(10358):1103-1116.

IMmotion-010: adjuvant Atezolizumab

Sub-analyses (no signal even in M1 NED, sarcomatoid, PD-L1+)



All patients	164/390	168/388	57·2 (44·6 to NE)	49·5 (47·4 to NE)	0·93 (0·75–1·15)
Age group , years					
<65	100/248	106/248	57·2 (48·4 to NE)	52·9 (47·4 to NE)	0·91 (0·69–1·19)
≥65	64/142	62/140	42·5 (29·3 to NE)	47·9 (29·4 to NE)	0·96 (0·68–1·36)
Race*					
White	141/324	129/304	57·2 (40·5 to NE)	49·5 (47·4 to NE)	1·00 (0·79–1·27)
Asian	12/43	28/51	NE (NE to NE)	33·1 (8·3 to NE)	0·41 (0·21–0·81)
Black	3/8	1/9	NE (5·6 to NE)	NE (NE to NE)	3·72 (0·38–36·09)
Sex					
Male	129/287	117/278	57·2 (36·1 to NE)	52·9 (47·9 to NE)	1·08 (0·84–1·39)
Female	35/103	51/110	NE (NE to NE)	49·1 (30·9 to NE)	0·61 (0·40–0·94)
Geographical region					
North America†	54/143	50/139	NE (48·4 to NE)	NE (47·9 to NE)	1·00 (0·68–1·47)
Rest of the world	110/247	118/249	57·2 (38·0 to NE)	49·1 (36·5 to NE)	0·90 (0·69–1·17)
Component of sarcomatoid					
Yes	18/37	37/67	NE (11·7 to NE)	23·0 (11·3 to NE)	0·77 (0·44–1·36)
No	146/353	131/321	57·2 (47·1 to NE)	49·6 (47·9 to NE)	1·00 (0·79–1·27)
PD-L1 expression					
IC0	71/158	63/153	NE (31·7 to NE)	52·9 (45·4 to NE)	1·08 (0·77–1·52)
IC1, 2, or 3	93/232	105/235	57·2 (44·6 to NE)	47·9 (38·6 to NE)	0·83 (0·63–1·10)
Disease status					
T2–T3a	87/252	89/248	NE (NE to NE)	NE (49·5 to NE)	0·93 (0·69–1·25)
T3b–c or T4 or N+	42/82	45/88	33·0 (26·3 to NE)	37·6 (18·2 to NE)	0·93 (0·61–1·41)
M1 NED	35/56	34/52	24·8 (14·0 to 47·1)	30·0 (15·9 to 45·4)	0·93 (0·58–1·49)
UISS risk score‡					
Intermediate to high risk	90/240	88/221	NE (NE to NE)	52·9 (49·1 to NE)	0·89 (0·67–1·20)
High risk	39/94	46/115	NE (33·0 to NE)	NE (37·9 to NE)	1·02 (0·67–1·57)
M1 NED	35/56	34/52	24·8 (14·0 to 47·1)	30·0 (15·9 to 45·4)	0·93 (0·58–1·49)

Pal SK, et al. Lancet 2023; 2022 Oct 1;400(10358):1103-1116.

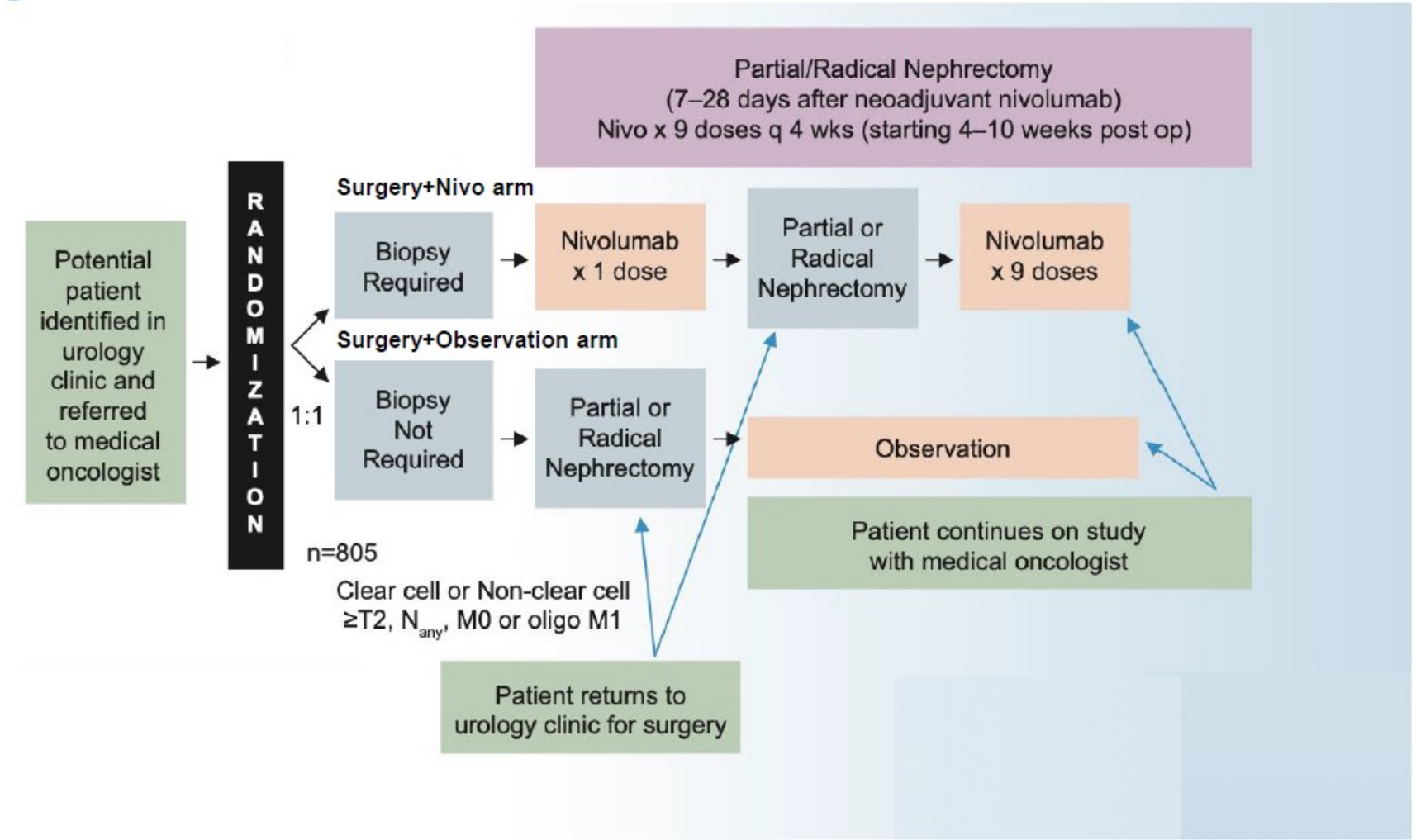
IMmotion-010: adjuvant Atezolizumab

Toxicities as expected

	Atezolizumab (n=390)				Placebo (n=383)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any	266 (68%)	96 (25%)	10 (3%)	1 (<1%)	257 (67%)	77 (20%)	4 (1%)	3 (1%)
Common adverse events								
Fatigue	107 (27%)	2 (1%)	0	0	91 (24%)	2 (1%)	0	0
Diarrhoea	80 (21%)	7 (2%)	0	0	77 (20%)	2 (1%)	0	0
Arthralgia	77 (20%)	1 (<1%)	0	0	56 (15%)	1 (<1%)	0	0
Pruritus	74 (19%)	0	0	0	47 (12%)	1 (<1%)	0	0
Hypothyroidism	56 (14%)	0	0	0	12 (3%)	0	0	0
Cough	50 (13%)	1 (<1%)	0	0	48 (13%)	0	0	0
Headache	48 (12%)	3 (1%)	0	0	47 (12%)	2 (1%)	0	0
Nausea	46 (12%)	0	0	0	54 (14%)	0	0	0
Rash	45 (12%)	1 (<1%)	0	0	20 (5%)	0	0	0
Pyrexia	43 (11%)	0	0	0	16 (4%)	0	0	0
Back pain	43 (11%)	0	0	0	44 (11%)	1 (<1%)	0	0

Pal SK, et al. Lancet 2023; 2022 Oct 1;400(10358):1103-1116.

PROSPER: Adjuvant Nivolumab (including brief neoadjuvant)



Allaf M, Kim SE, Harshman LC, et al. ESMO Congress 2022

PROSPER: Adjuvant Nivolumab (including brief neoadjuvant)

Patient Characteristics Post Surgery

- >60% had pT3/T4 tumors
- >60% had high grade tumors
- ~80% had clear cell RCC
- ~ 5% in each group underwent partial nephrectomy
- ~3% of RCC patients that had surgery were not disease-free post surgery
- ~ 5% were non-RCC cases that were excluded from the primary analysis

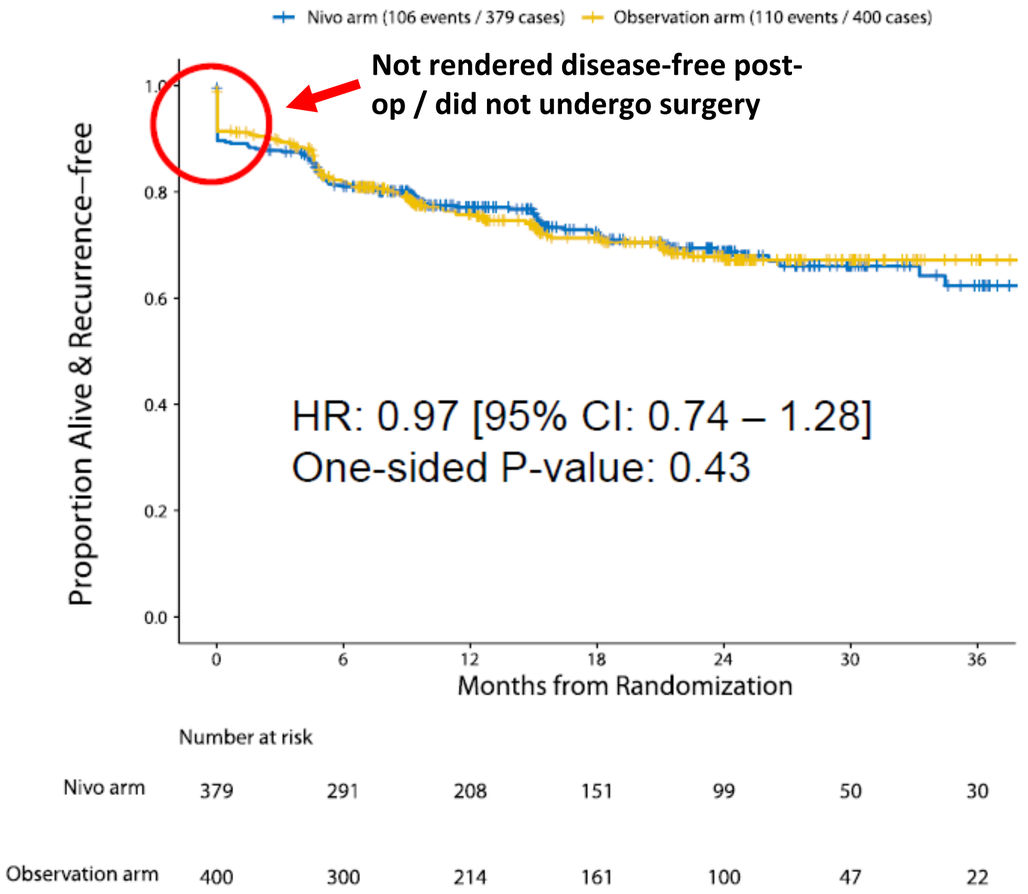
	Surgery+Nivo arm n = 404	Surgery+Observation arm n = 415	Total n = 819
	N (%)	N (%)	N (%)
Pathologic T-stage			
T1	35 (10)	42 (11)	77 (10)
T2	83 (24)	81 (21)	164 (22)
T3 or T4	233 (66)	261 (68)	494 (67)
Pathologic N-stage			
Nx/N0	316 (90)	355 (92)	671 (91)
N1	36 (10)	30 (8)	66 (9)
Pathologic M-stage			
Mx/M0	340 (97)	368 (96)	708 (96)
M1	12 (3)	16 (4)	28 (4)
Surgery Type			
Radical	344 (96)	375 (95)	719 (95)
Surgery Histology			
Clear cell	278 (78)	306 (77)	584 (77)
Papillary	27 (8)	20 (5)	47 (6)
Chromophobe	24 (7)	21 (5)	45 (6)
Sarcomatoid features			
Yes	30 (8)	49 (12)	79 (11)
Fuhrman grade			
1	14 (4)	10 (3)	24 (4)
2	89 (28)	96 (27)	185 (28)
3	136 (42)	146 (41)	282 (42)
4	81 (25)	100 (28)	181 (27)

Allaf M, Kim SE, Harshman LC, et al. ESMO Congress 2022

PROSPER: Adjuvant Nivolumab (including brief neoadjuvant)

- At interim analysis, DSMC stopped trial for inefficacy
- Median Follow-up=16months
- No difference in RFS between arms
- OS data not mature

- **Conditional power for primary and sensitivity analyses <30%**
- **Trial was quickly approaching full-information when this decision was made (71.8% information)**

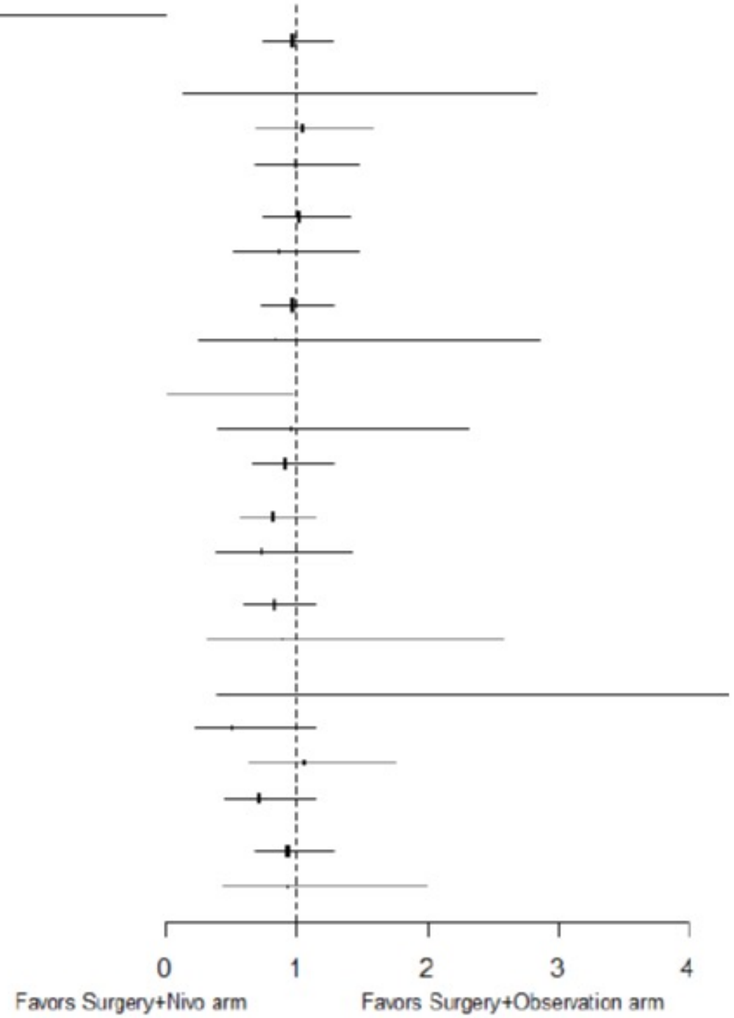


Allaf M, Kim SE, Harshman LC, et al. ESMO Congress 2022

PROSPER: Adjuvant Nivolumab (including brief neoadjuvant)

Sub-analyses

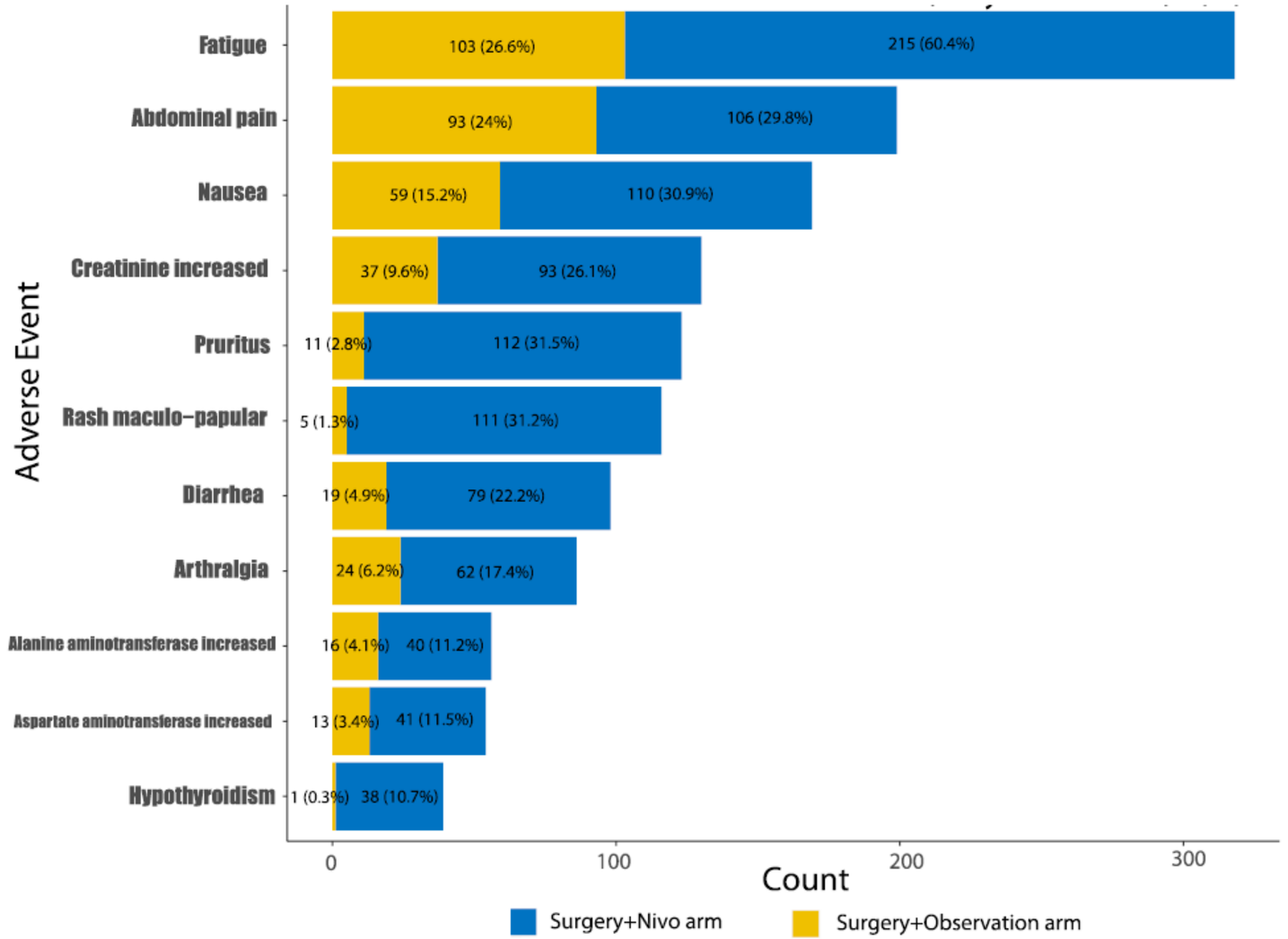
Sub-group	N	HR	95% CI
All RCC Patients	779	0.97	(0.74, 1.27)
cT1	25	0.61	(0.13, 2.83)
cT2	398	1.05	(0.69, 1.59)
cT3 or cT4	394	1.00	(0.68, 1.47)
cNx or cN0	697	1.02	(0.74, 1.40)
cN1	121	0.87	(0.51, 1.47)
cMx or cM0	790	0.97	(0.73, 1.28)
cM1	27	0.85	(0.25, 2.86)
pTx or pT1	79	0.12	(0.01, 0.96)
pT2	164	0.96	(0.40, 2.31)
pT3 or pT4	494	0.91	(0.65, 1.28)
pNx or pN0	671	0.81	(0.57, 1.14)
pN1	66	0.73	(0.37, 1.41)
pMx or pM0	708	0.83	(0.60, 1.14)
pM1	28	0.89	(0.31, 2.57)
Fuhrman Grade 1	24	3.37	(0.38, 30.18)
Fuhrman Grade 2	185	0.50	(0.21, 1.15)
Fuhrman Grade 3	282	1.06	(0.63, 1.76)
Fuhrman Grade 4	181	0.72	(0.45, 1.14)
Clear-cell	625	0.93	(0.68, 1.28)
Non-clear cell	128	0.93	(0.44, 1.99)



Allaf M, Kim SE, Harshman LC, et al. ESMO Congress 2022

PROSPER: Adjuvant Nivolumab (including brief neoadjuvant)

Toxicities as expected



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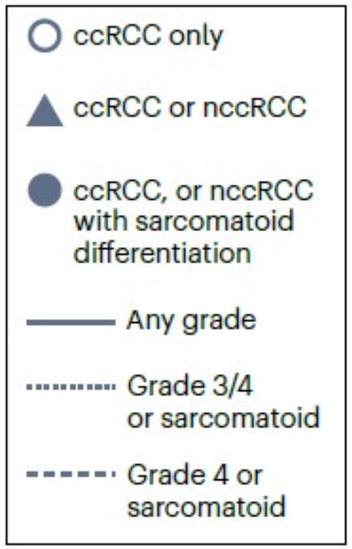
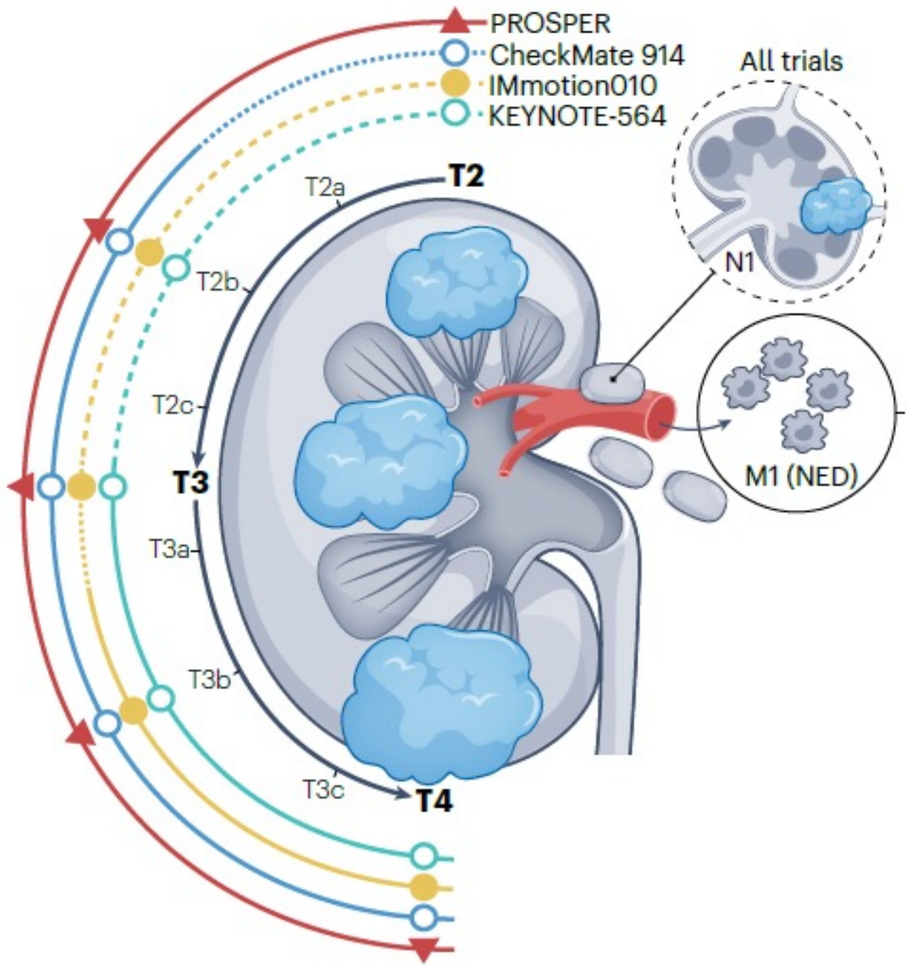
Potential reasons for discordant results with adjuvant ICIs

Differences in eligibility criteria





PROSPER
- Synchronous nephrectomy and metastatectomy
- Metachronous nephrectomy and metastatectomy within 12 weeks
- Patients with >3 metastases or with bone, brain or liver metastasis were excluded

CheckMate 914
- Patients with NED after metastastectomy were not included

IMmotion010
- Synchronous nephrectomy and metastatectomy of lung or adrenal metastases
- Metachronous metastatectomy of lung, lymph node or soft-tissue metastases >1 year after nephrectomy

KEYNOTE-564
- Synchronous nephrectomy and metastatectomy
- Metachronous nephrectomy and metastatectomy within 1 year
- Patients with bone or brain metastases were excluded

Labaki C, Choueiri TK. Nat Rev Clin Oncol 2023; Volume 20 | February 2023 | 65–66 |

Potential reasons for discordant results with adjuvant ICIs

Excessive toxicities (IPI-NIVO)

	NIVO+IPI (n = 404)	Placebo (n = 407)
Median duration of therapy (range), months	5.1 (< 0.1-8.3)	5.1 (< 0.1-8.1)
Q1, Q3	2.8, 5.3	5.1, 5.3
Median number of doses received (range)	NIVO, 12 (1-12) IPI, 4 (1-4)	12 (1-12)[a] 4 (1-4)[b]
Completed all 12/4 doses of NIVO/IPI, n (%)	**231 (57)**	**361 (89)**
Discontinued treatment, n (%)[c]	**173 (43)**	**46 (11)**
Discontinued due to study drug toxicity, n (%)	132 (33)	5 (1)
All-cause AEs, n (%)[d]	**392 (97)**	**361 (89)**
Grade ≥ 3	155 (38)	42 (10)
Led to treatment discontinuation	129 (32)	9 (2)
Treatment-related AEs, n (%)[d]	**359 (89)**	**231 (57)**
Grade ≥ 3	115 (28)	8 (2)
Led to treatment discontinuation[e]	117 (29)	4 (1)
Deaths due to study drug toxicity, n (%)	4 (1)[f]	0

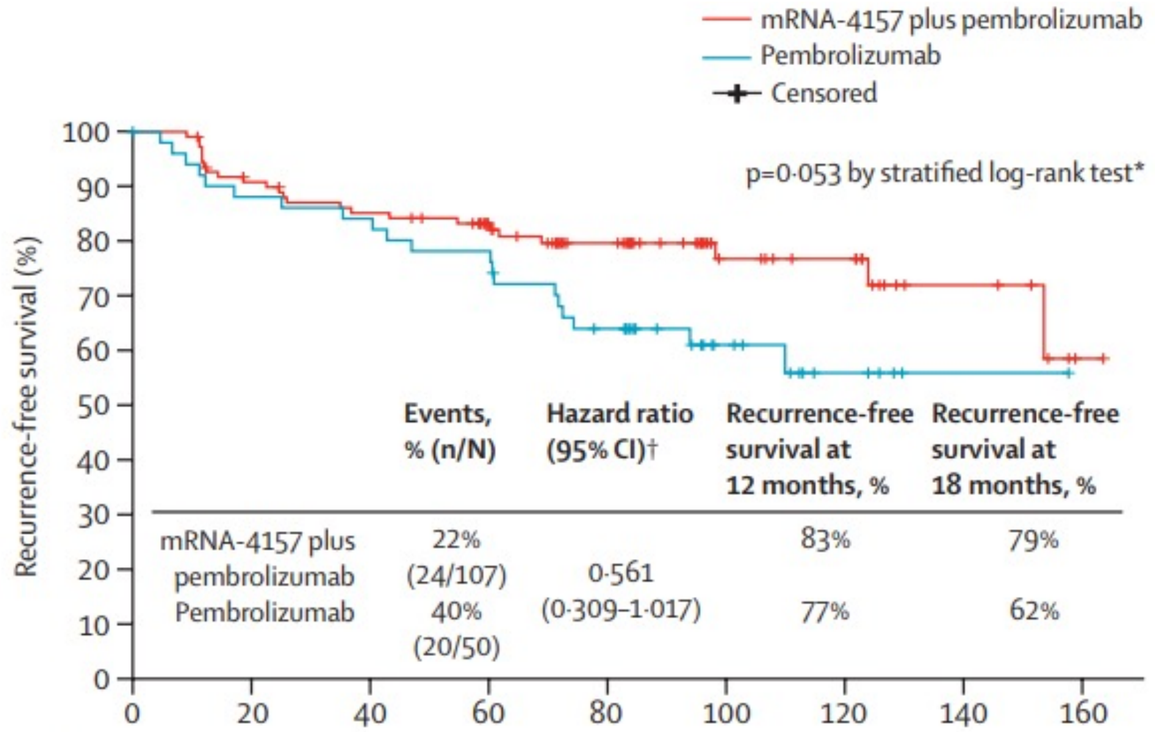
Motzer R, et al. ESMO 2022. CHECKMATE-914

Ongoing phase III trials of adjuvant therapy for RCC

Trial	Histology	Eligibility	Control	Experimental
LITESPARK-002	Clear cell	≥pT2 Grade 4, including M1 NED (synchronous or metachronous within 2 years)	Pembro-Placebo	Pembro-Belzutifan
RAMPART	Clear cell	Leibovich score 3-11 (stop recruiting intermediate risk 3-5 after 3 years or when 25% of target	Observation	Durva or Durva+Treme
STRIKE (ALLIANCE)	Clear cell	TBD	Pembro	Pembro + Tivozanib
NCT06146777 (Sun Yat-Sen)	Non-clear cell (papillary)	III	Placebo	Pembro

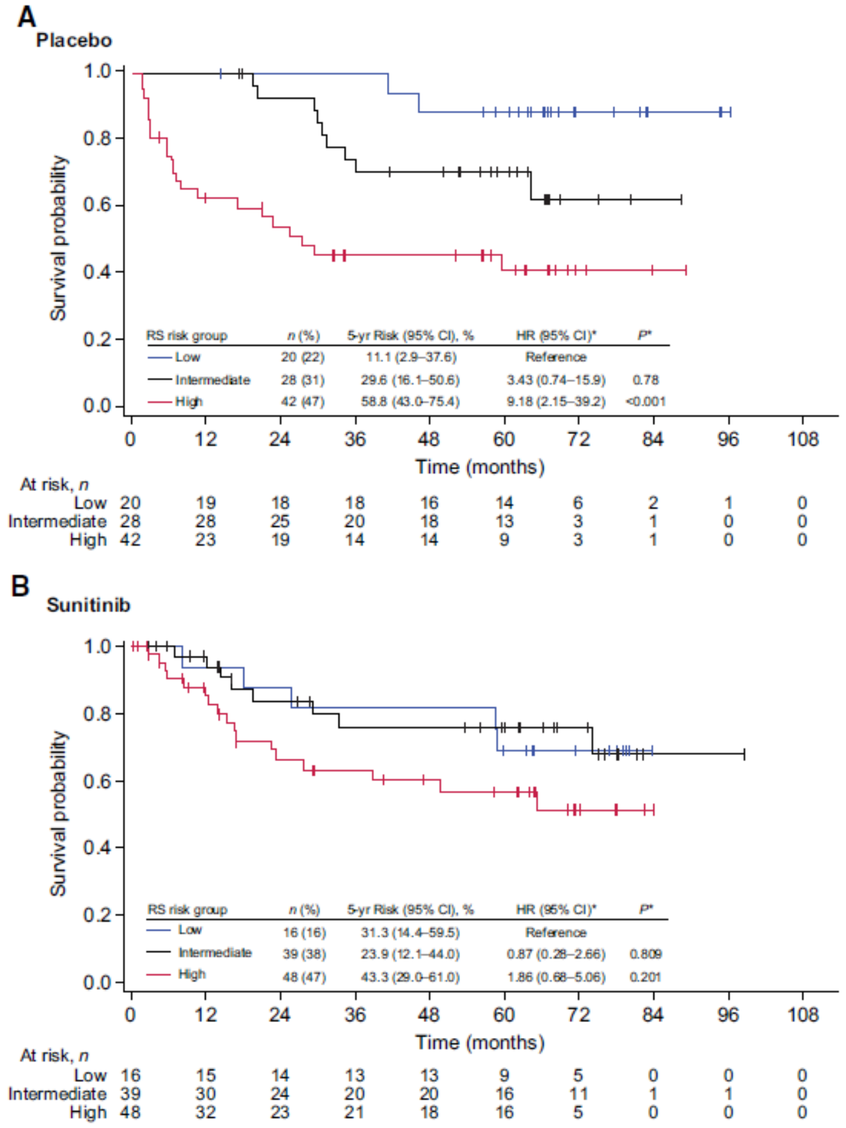
Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942): a randomised, phase 2b study

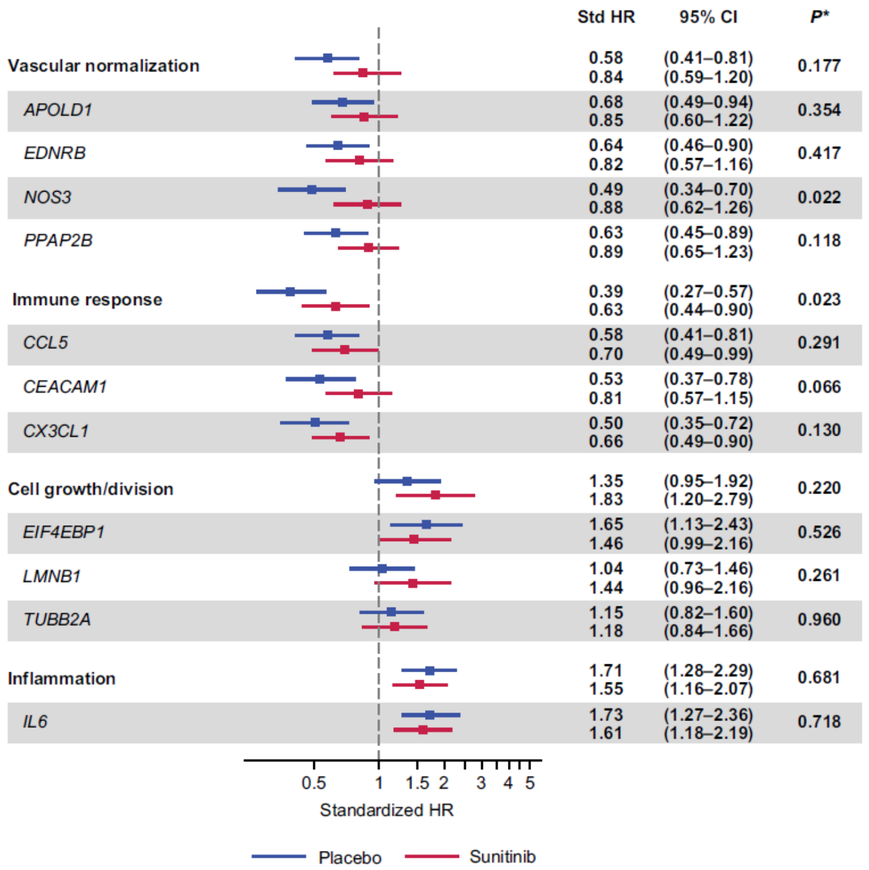
Jeffrey S Weber, Matteo S Carlino, Adnan Khattak, Tarek Meniawy, George Ansstas, Matthew H Taylor, Kevin B Kim, Meredith McKean, Georgina V Long, Ryan J Sullivan, Mark Faries, Thuy T Tran, C Lance Cowey, Andrew Pecora, Montaser Shaheen, Jennifer Segar, Theresa Medina, Victoria Atkinson, Geoffrey T Gibney, Jason J Luke, Sajeve Thomas, Elizabeth I Buchbinder, Jane A Healy, Mo Huang, Manju Morrissey, Igor Feldman, Vasudha Sehgal, Celine Robert-Tissot, Peijie Hou, Lili Zhu, Michelle Brown, Praveen Aanur, Robert S Meehan, Tal Zaks**



Lancet 2024 Jan 18:S0140-6736(23)02268-7.

Molecular (gene expression) Prognostic model to select for adjuvant therapy?



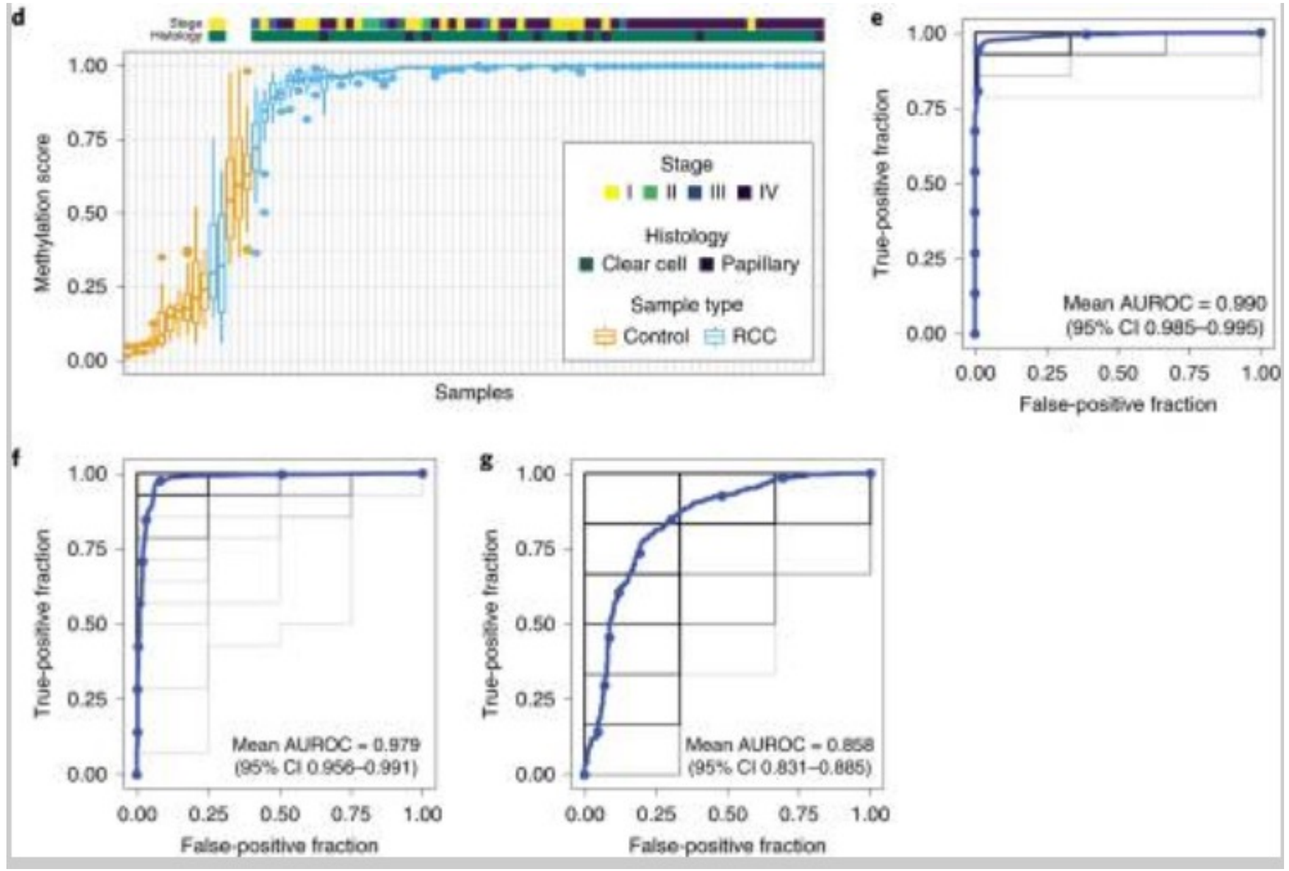


A 16-gene expression (RNA) recurrence score (RS) signature consisting of 11 cancer-specific and 5 reference genes, was developed using archived, formalin-fixed, paraffin embedded (FFPE) tumor tissue from patients with stage I–III RCC who underwent nephrectomy at Cleveland Clinic.

RS results predicted outcomes (TTR primary) in both arms of S-TRAC, with the strongest results observed in the placebo arm. When high versus low RS groups were compared, HR for recurrence was 9.18 in the placebo arm; interaction of RS with treatment was not significant **(22% of patients in S-TRAC were classified as low risk by the RS with a 5-year recurrence risk of 11%)**

Rini B, CCR 2018

Post-operative molecular residual disease to inform therapy



- cfDNA in < 80% of advanced RCC and false positive possible from clonal hematopoiesis or germline alterations.
- cfMeDIP-seq (cell-free methylated DNA immunoprecipitation and high-throughput sequencing assay) for detection of RCC.
- **Top 300 differentially methylated regions (DMRs), was used to assign a methylation score**.
- cfMeDIP-seq had a mean **AUROC of 0.979 for plasma DNA and 0.858 for correctly classifying urine DNA** (2/3 of RCC patients had localized disease).
- While urine-based classification was not as accurate as plasma, performance can be **improved through utilizing tumor methylation to inform cfDNA methylation** analysis.

Nuzzo P, et al. Nat Med 2020

Utility of circulating tumor (ct)DNA testing for molecular residual disease (MRD) detection and treatment response monitoring in patients (pts) with renal cell carcinoma (RCC)

Michael Smigelski[1], Sumedha Sudharman[2], Shavy Nagpal[1], Bailey Brooks[3], Thomas Gerald[3], Ricardo Sanchez-Mendez[1], Cristina Battista[3], Raj Bhanvadia[3], Austin Kazarian[3], Sharon Choi[4], Carcia Carson[2], Tamara Mahmood[2], Elshaddai Z. White[2], Adam ElNaggar[2], Minetta C. Liu[2], Meredith R. Metcalf[1], Rana R. McKay[4], Anthony Corcoran[5], Vitaly Margulis[3], William C. Huang[1]

[1]Department of Urology, NYU Grossman School of Medicine, New York, USA; [2]Natera, Inc, Austin, TX, USA; [3]Department of Urology, UT Southwestern, Dallas, TX, USA; [4]University of California San Diego, Moores Cancer Center, San Diego, CA, USA; [5]Department of Urology, NYU Long Island School of Medicine, New York, USA

Tumor-informed ctDNA assay (Signatera™)

Table 1. Patient & tumor characteristics

Characteristic	N = 63[1]
Median age (years)	64 (21 - 87)
Gender	
Male	46 (73%)
Female	17 (27%)
Subtype	
Clear cell	51 (81%)
Non-clear cell	9 (14%)
Unclassified	3 (5%)
Number of recurrences	12 (19%)

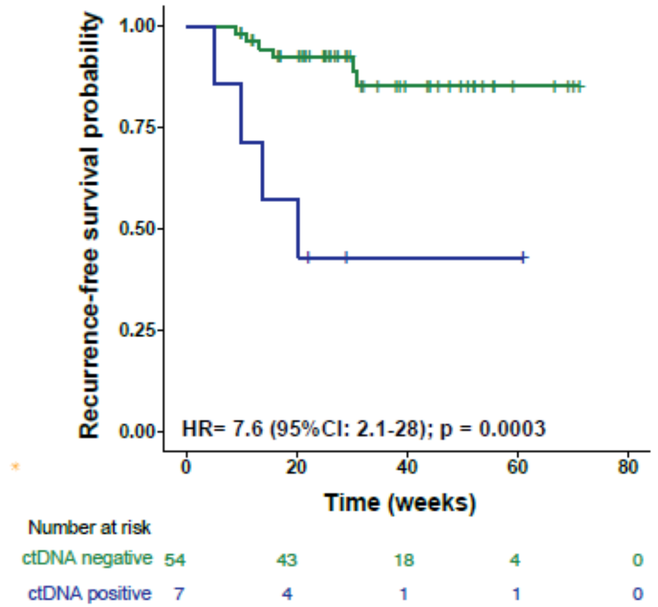
Characteristic	N = 63[1]
Risk group classification*	51/63
Intermediate-high	42 (65%)
High	3 (7%)
M1 NED#	3 (7%)
Unknown	3 (5%)
Adjuvant Treatment	23/63 (37%)
Immunotherapy	20 (32%)
TKI	2 (3%)
Immunotherapy/TKI	3 (5%)

Characteristic	N = 63[1]
Clinical stage	
I	1 (2%)
II	4 (6%)
III	52 (83%)
IV	6 (9%)
Median follow-up post-surgery (weeks)	43.9 (22.9-84.1)

[1]Median (Range); n (%)

*Risk group classification based on Keynote 564 trial[3]
#M1 (Resection of the primary tumor and solid, isolated, soft-tissue metastases) with no evidence of disease (NED)

Figure 3. Association of ctDNA status with RFS within the MRD window



- Overall, these results **demonstrate the predictive value of MRD using tumor-informed ctDNA in patients with RCC.**
- Future **prospective studies in RCC are warranted** to validate the utility of ctDNA in informing clinical decision-making to select high-risk patients for adjuvant therapy.

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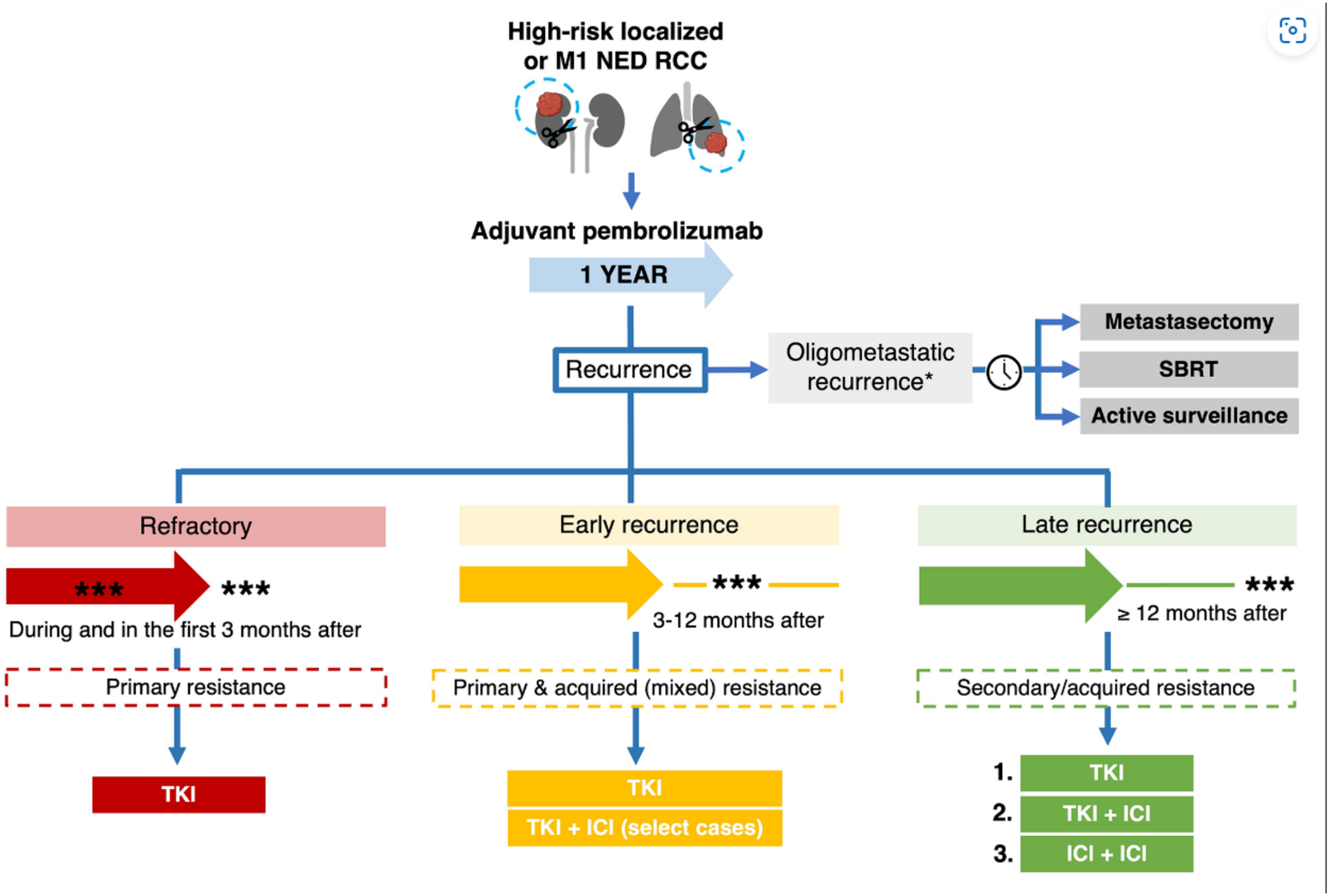
Using Clinical Characteristics to Guide Treatment of Recurrent RCC After Adjuvant Pembrolizumab



Maria T. Bourlon, MD, MS; Paola Valdez, MD; Toni Choueiri, MD, FASCO; and Elaine Lam, MD.. ASCO POST 10 January 2024

Adjuvant therapy of RCC: Take home message

- Clinical trials evaluating immunotherapy and VEGFR TKIs for RCC in the adjuvant setting have yielded **conflicting data** for DFS benefit (**none have shown prolonged OS yet**).
- **Pembrolizumab** is currently approved for the adjuvant setting in RCC in the USA and Europe based on the results of the KEYNOTE-564 trial (improved DFS HR 0.72 and OS HR 0.62).
- The success of pembrolizumab in the context of multiple negative ICI trials is unclear (nivo, atezo, IPI-NIVO), but may be partly from patient selection (higher risk, PD1 vs. PD-L1 inh, safety profile, duration)
- **Sunitinib** is approved by the US FDA for the adjuvant treatment of high risk RCC (improved DFS HR 0.76, no improvement of OS).
- **Adjuvant therapy may be offered to appropriate patients after discussing benefits and risks**.
- The utility of **novel adjuvant combination therapies** including HIF2α blockade (belzutifan) or VEGF inhibitor (Tivozanib) with pembrolizumab will be explored in Phase III trials.
- Impact of adjuvant pembro on therapy for metastatic recurrence needs study (VEGF+/-IO)
- **Appropriate patient selection using clinical prognostic factors, molecular residual disease (MRD) information and predictive biomarkers is needed to develop precision adjuvant therapy and achieve better therapeutic index**.

Thank you!

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