

#guardsymposium2026
X @GuardConsortium



GUARD INTERNATIONAL SYMPOSIUM

GU-Alliance for Research and Development

PRESENCIAL RETRANSMITIDO EN DIRECTO
FACE-TO-FACE AND LIVE STREAMING



16-18 SEPTIEMBRE 2026

Espacio Maldonado, Madrid



Gemelli



Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore



Current status of adjuvant therapy in HR-ccRCC

Roberto Iacovelli

Agenda

Why adjuvant immunotherapy for RCC is a milestone in oncology?

What about adjuvant immunotherapy for RCC?

How to define high-risk RCC?

What we learnt from KN564 trial?

How to improve adjuvant pembrolizumab?

Safety profile.

Why pembrolizumab was a milestone for RCC?



In the past years, some studies tried to investigate adjuvant Tx for high risk-RCC. Those started immediately after the first evidences supporting IFN for mRCC and continued during TKI's era.

NO one was positive with exclusion of S-TRAC: DFS HR 0.76 (95%CI, 0.59-0.98; p=0.03 & NO OS benefit)¹.

Before and after **S-TRAC**, other trials continued to fail using other TKI and mTORi: ASSURE (sorafenib & sunitinib)², SORCE (sorafenib)³, PROTECT (pazopanib)⁴, ATLAS (axitinib)⁵, and EVEREST (everolimus)⁶

Improvements in adjuvant therapy have always been considered a step forward in oncology: this means the possibility of saving lives—not “just” treating cancer.

1. Ravaud A, et al. N Engl J Med 2016;375:2246-2254
2. Haas NB, Lancet. 2016 May 14;387(10032):2008-16.
3. Eisen T, et al. J Clin Oncol. 2020 Dec 1;38(34):4064-4075.
4. Motzer RJ, et al. J Clin Oncol. 2017 Dec 10;35(35):3916-3923.
5. Gross-Goupil M, et al. Ann Oncol. 2018 Dec 1;29(12):2371-2378.
6. Ryan CW, et al. Lancet. 2023 Sep 23;402(10407):1043-1051.

What about adjuvant immunotherapy for RCC?

Study and outcome	IMmotion010 ¹ Atezo vs. pbo	CheckMate914 ² Ipi/nivo vs. pbo	CheckMate914 ³ Nivo vs. pbo	PROSPER ⁴ Nivo vs. pbo	KN564 ⁵ Pembro vs. pbo	RAMPART Dur+Tre vs. pbo
Patients	390 vs. 388	405 vs. 411	411 vs. 208	404 vs. 415	496 vs. 498	225 vs. 340
mFU (mos)	44.7	37.0	27.0	16.0	57.2	36.0
Clear cell (%)	93.3 vs. 91.8	100 vs. 100	100 vs. 100	78 vs. 77	100 vs. 100	84.9 vs. 83.8
<T3 (%)		15 vs. 15	11 vs. 12	29 vs. 30 ^c		25.5 vs. 23.3
T3 (%)	65 vs. 64 ^a	78 vs. 77	82 vs. 81	57 vs. 63 ^d	85.1 vs. 86.9 ^e	73.3 vs. 76.1
T4 -N+ (%)	21 vs. 23 ^b	7 vs. 8	7 vs. 7		8.1 vs. 7.4	4.1 vs. 6.7 ^f
M1NED (%)	14.4 vs 13.4	NA vs. NA	NA vs. NA		5.8 vs. 5.6	
mDFS (mos)	57.2 vs. 49.5	NR vs. 50.7	NR vs. NR	NR vs. NR	NR vs. NR	NR vs. NR
HR (95%CI)	0.93 (0.75-1.15)	0.92 (0.71-1.19)	0.80 (0.58-1.12)	0.94 (0.74-1.21)	0.72 (0.59-0.87)	0.65 (0.45-0.93)
mOS (mos)	NR vs. NR	47.2 vs. 40.8	NA vs. NA	NA vs. NA	NA vs. NA	NA
HR (95%CI)	0.97 (0.67-1.42)	0.84 (0.71-0.99)		1.28 (0.84-1.95)	0.62 (0.44-0.87)	

Legend:

- a) T2-T3a
- b) T3b-N+
- c) Includes Tx and T1 9% vs 10%
- d) Includes T3 and T4
- e) Includes T2G4 and T3
- f) Only N+; T4 were 1.4 vs. 0.6

- 1. Pal SK, et al. Lancet. 2022 Oct 1;400(10358):1103-1116.
- 2. Motzer RJ, et al. Lancet. 2023 Mar 11;401(10379):821-832.
- 3. Bourlon MT, ASCO-GU2024
- 4. Allaf ME et al. Lancet Oncol. 2024 Aug;25(8):1038-1052.
- 5. Choueiri TK, ASCO GU 2024
- 6. Larkin J, et al. presented at ESMO 2025

What about adjuvant immunotherapy for RCC?

Study and outcome	IMmotion010 ¹ Atezo vs. pbo	CheckMate914 ² Ipi/nivo vs. pbo	CheckMate914 ³ Nivo vs. pbo	PROSPER ⁴ Nivo vs. pbo	KN564 ⁵ Pembro vs. pbo	RAMPART Dur+Tre vs. pbo
Patients	390 vs. 388	405 vs. 411	411 vs. 208	404 vs. 415	496 vs. 498	225 vs. 340
mFU (mos)	44.7	37.0	27.0	16.0	57.2	36.0
Clear cell (%)	93.3 vs. 91.8	100 vs. 100	100 vs. 100	78 vs. 77	100 vs. 100	84.9 vs. 83.8
<T3 (%)		15 vs. 15	11 vs. 12	29 vs. 30 ^c		25.5 vs. 23.3
T3 (%)	65 vs. 64 ^a	78 vs. 77	82 vs. 81	57 vs. 63 ^d	85.1 vs. 86.9 ^e	73.3 vs. 76.1
T4 -N+ (%)	21 vs. 23 ^b	7 vs. 8	7 vs. 7		8.1 vs. 7.4	4.1 vs. 6.7 ^f
M1NED (%)	14.4 vs 13.4	NA vs. NA	NA vs. NA		5.8 vs. 5.6	
mDFS (mos) HR (95%CI)	57.2 vs. 49.5 0.93 (0.75-1.15)	NR vs. 50.7 0.92 (0.71-1.19)	NR vs. NR 0.80 (0.58-1.12)	NR vs. NR 0.94 (0.74-1.21)	NR vs. NR 0.72 (0.59-0.87)	NR vs. NR 0.65 (0.45-0.93)
mOS (mos) HR (95%CI)	NR vs. NR 0.97 (0.67-1.42)	47.2 vs. 40.8 0.84 (0.71-0.99)	NA vs. NA	NA vs. NA 1.28 (0.84-1.95)	NA vs. NA 0.62 (0.44-0.87)	NA

Legend:

- a) T2-T3a
- b) T3b-N+
- c) Includes Tx and T1 9% vs 10%
- d) Includes T3 and T4
- e) Includes T2G4 and T3
- f) Only N+; T4 were 1.4 vs. 0.6

- 1. Pal SK, et al. Lancet. 2022 Oct 1;400(10358):1103-1116.
- 2. Motzer RJ, et al. Lancet. 2023 Mar 11;401(10379):821-832.
- 3. Bourlon MT, ASCO-GU2024
- 4. Allaf ME et al. Lancet Oncol. 2024 Aug;25(8):1038-1052.
- 5. Choueiri TK, ASCO GU 2024
- 6. Larkin J, et al. presented at ESMO 2025

How to define HR RCC eligible to adjuvant Tx?

SSIGN Score for Renal Cell Carcinoma (RCC)

Predicts progression of clear cell renal cell carcinoma after radical nephrectomy.

Pearls/Pitfalls ▾

Pathological T category As per 2002 TNM staging guidelines	pT1	0
	pT2	+1
	pT3a-c	+2
	pT4	+4

Regional lymph node status As per 2002 TNM staging guidelines	pNx or pN0		0
	pN1 or pN2		+2

Metastasis category As per 2002 TNM staging guidelines	M0	0	M1	+4
---	----	---	----	----

Tumor size	<5 cm		0	≥5 cm	+2
------------	-------	--	---	-------	----

Tumor (nuclear) grade	1 or 2	0	3	+1	4	+3
-----------------------	--------	---	---	----	---	----

Tumor necrosis present	No	0	Yes	+2
------------------------	----	---	-----	----

5 points

74.1% 5-year estimated cancer-specific survival.

UCLA Integrated Staging System (UISS) for Renal Cell Carcinoma (RCC)

Provides 5-year disease-free prognosis for localized and metastatic RCC.

Instructions ▾

When to Use ▾ Pearls/Pitfalls ▾ Why Use ▾

Type of disease present

Metastatic

Localized

UISS Criteria

Localized disease - T stage

T1

T2

T3

T4

Fuhrman nuclear grade

I

II

III

IV

ECOG Performance Status

0

≥1

Moderate Risk

80.4% Five year survival

Copy Results

Next Steps >>

ASSURE Nomogram

60 yo
Clear cell RCC, 4.5 cm
Vein invasion, G3, N0,
No necrosis, no sarcomatoid

Disease Free Survival (DFS) Probability										
1-year	2-year	3-year	4-year	5-year	6-year	7-year	8-year	9-year	10-year	
94.1%	87.2%	81.2%	76.0%	71.5%	67.6%	64.1%	61.0%	58.1%	55.6%	

Overall Survival (OS) Probability										
1-year	2-year	3-year	4-year	5-year	6-year	7-year	8-year	9-year	10-year	
99.6%	98.3%	96.4%	94.3%	92.1%	89.8%	87.6%	85.4%	83.2%	81.1%	

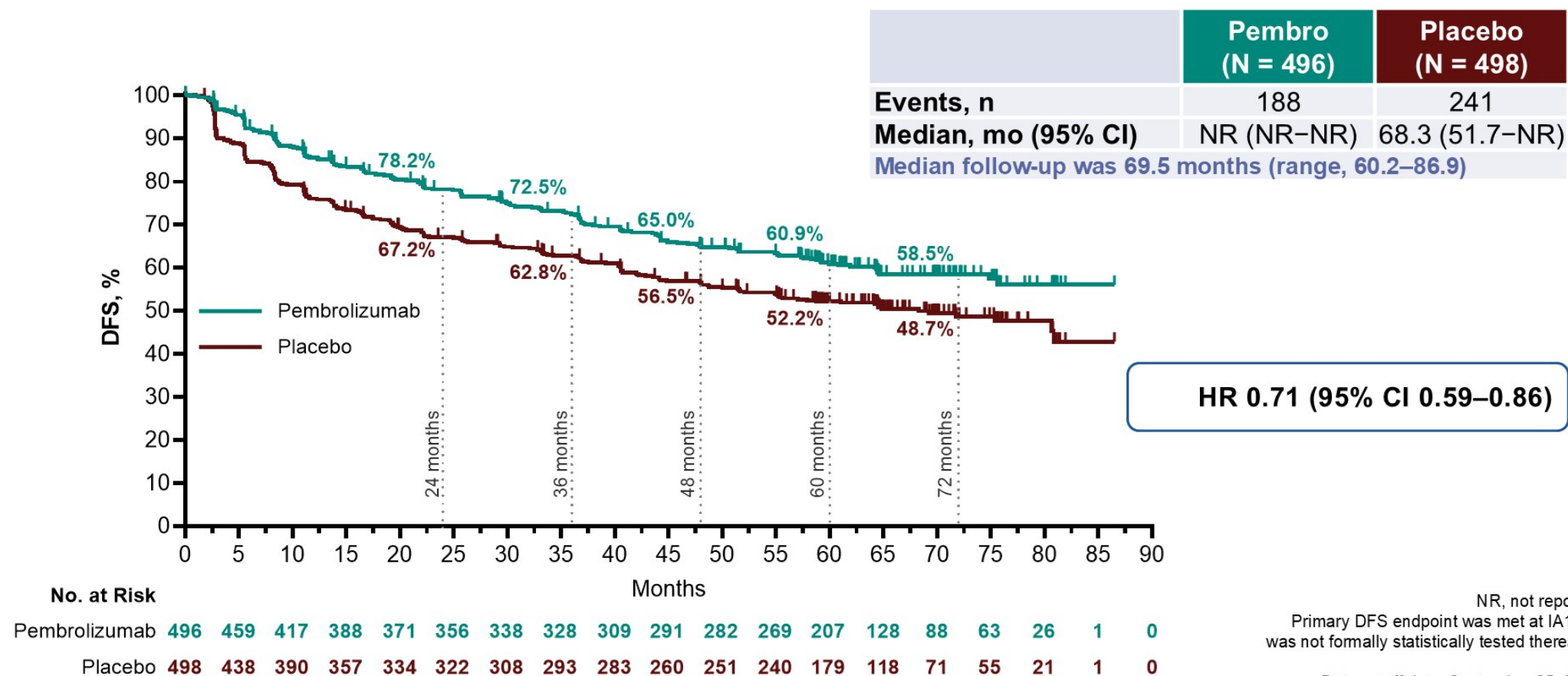
How to define HR RCC eligible to adjuvant Tx?

The KN564 classification:

<i>Parameter</i>	Intermediate –High Risk		High Risk		M1 NED
pT	pT2	pT3	pT4	Any	NED after surgical resection of metastases within 1 year from previous nephrectomy
pN	pN0	pN0	pN0	pN+	
M	M0	M0	M0	M0	
Grade	G4 or sarcomatoid	Any G	Any G	Any G	

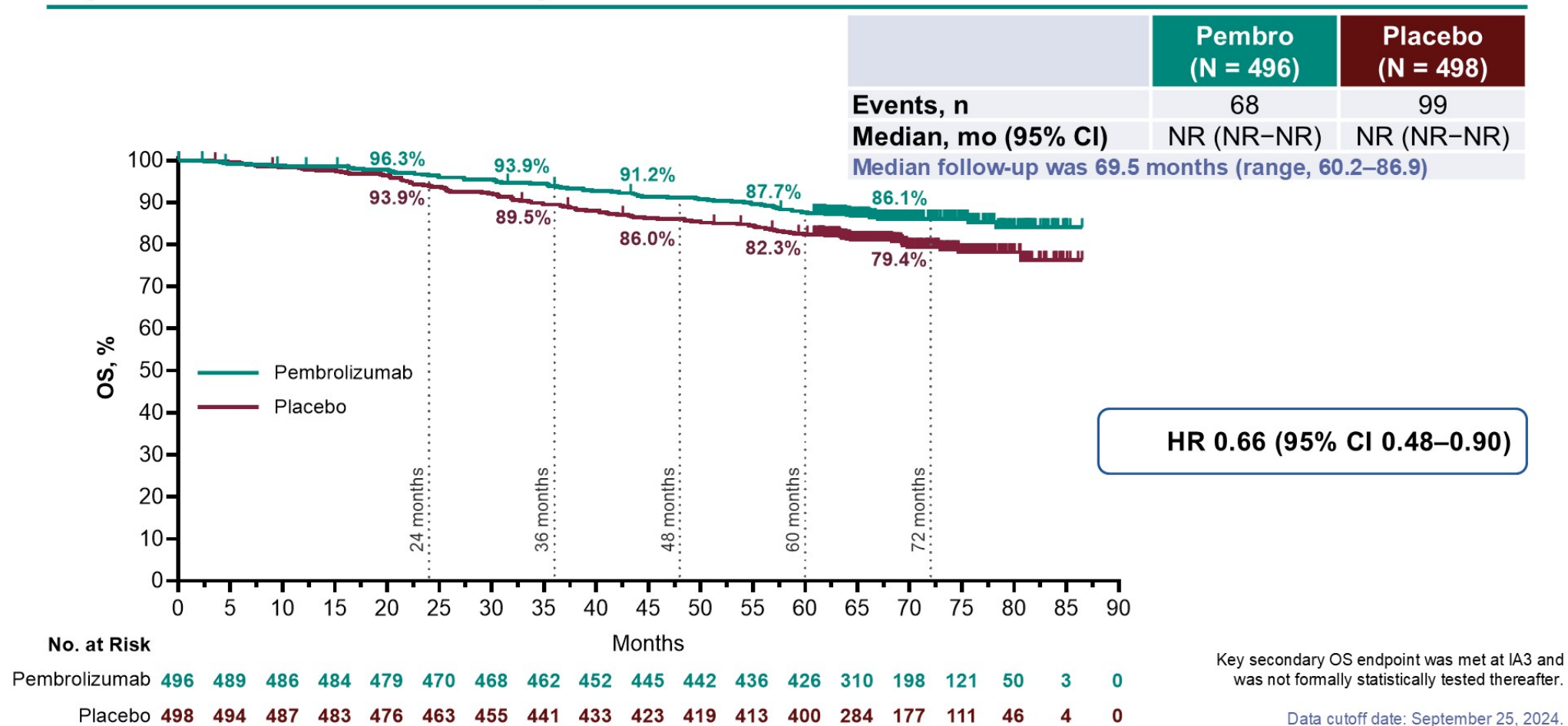
Why pembrolizumab is the standard of care?

Updated DFS by Investigator, ITT Population

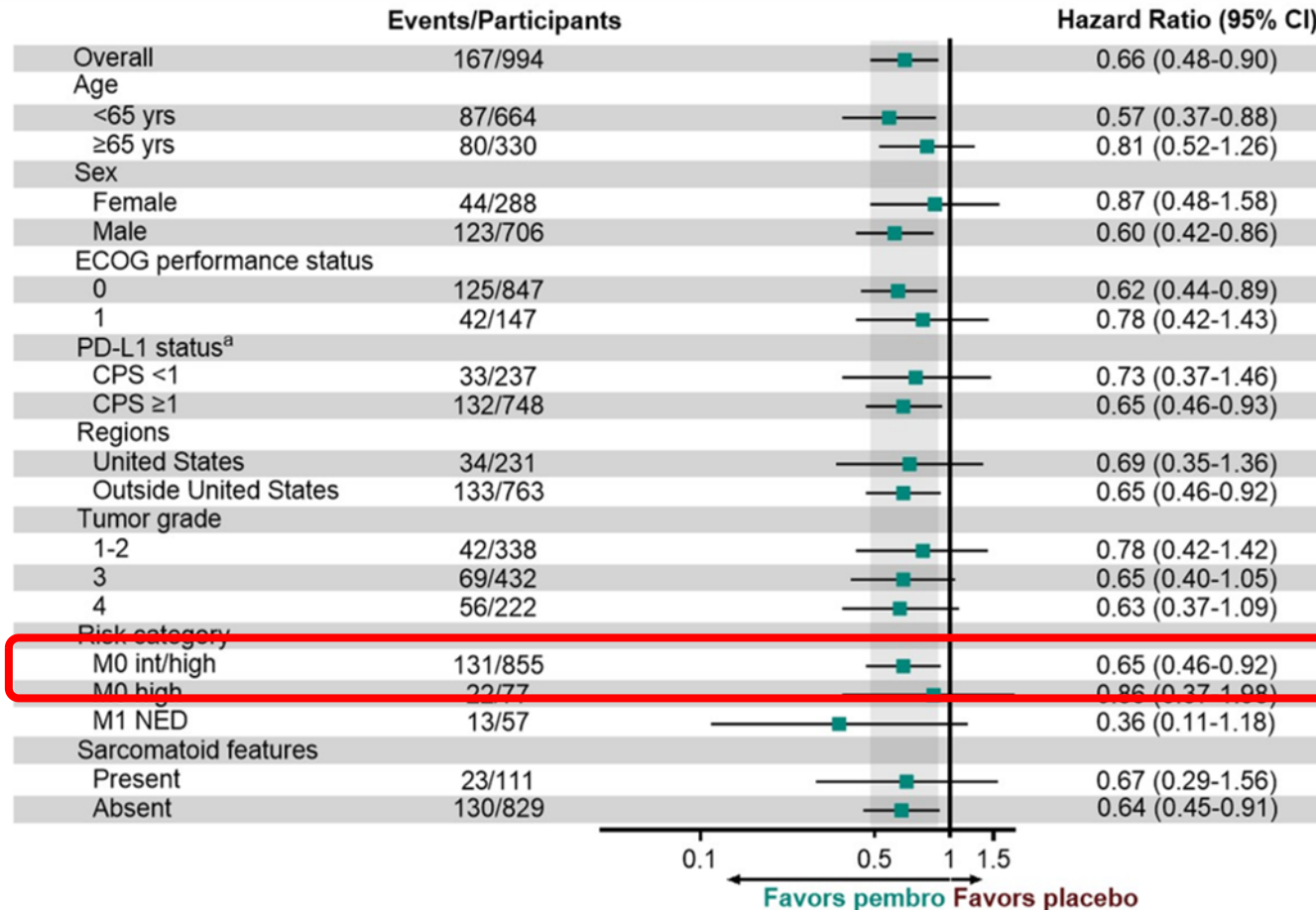


Why pembrolizumab is the standard of care?

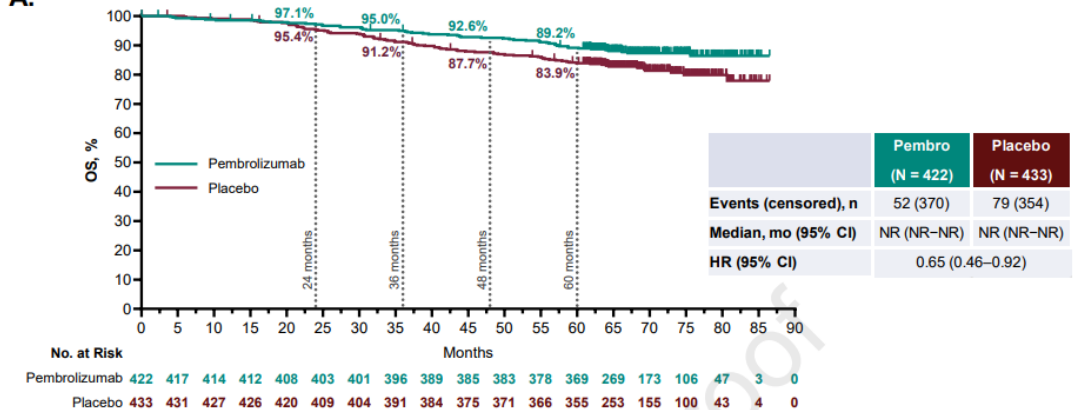
Updated OS, ITT Population



Why pembrolizumab is the standard of care?

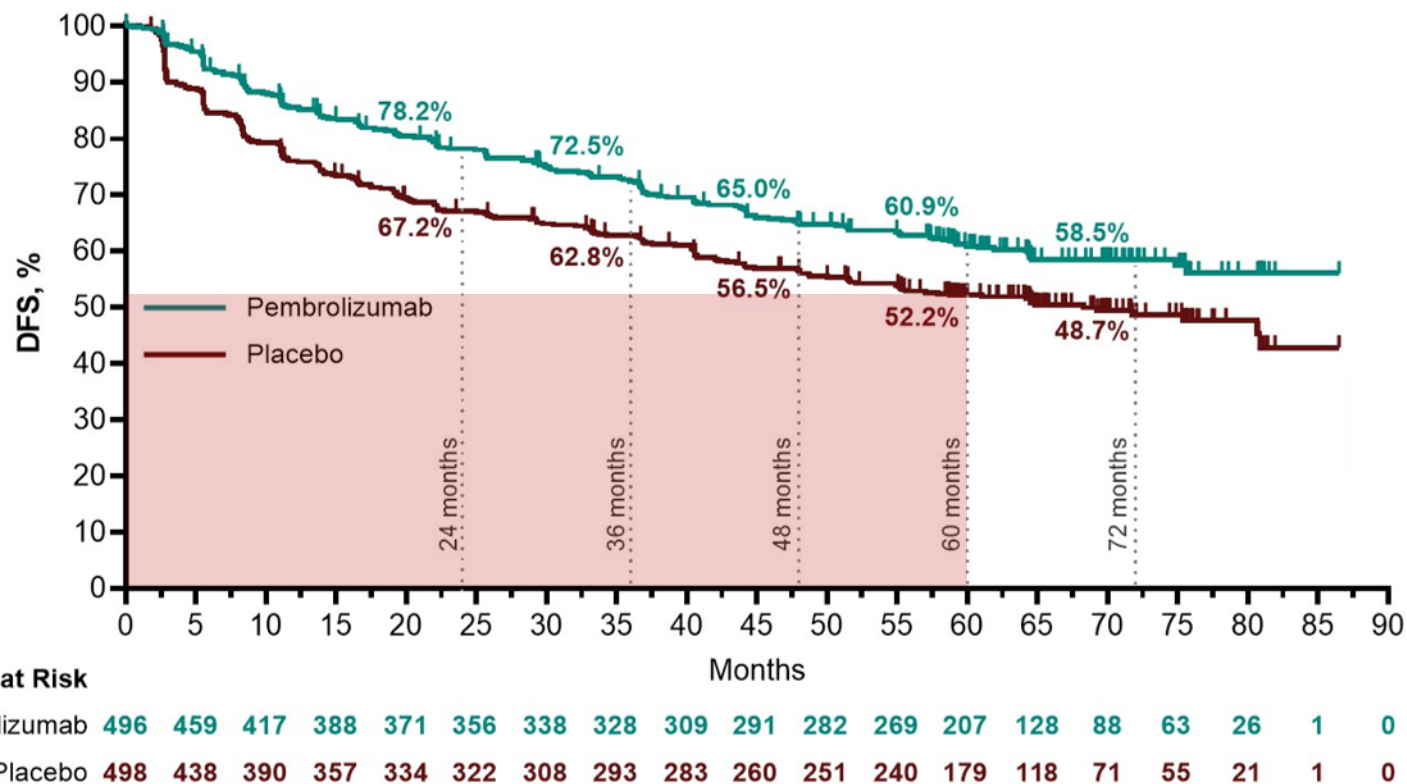


A.



The **largest population (86%)** with pT2N0G4 and pT3N0anyG (86%) had a **well evident benefit from adjuvant pembrolizumab.**

Was the HR definition reliable?



The KN564 classification was able to define a **population with ≈50% of risk of progression at 5y**

How to improve adjuvant pembrolizumab?

Study Design: LITESPARK-022 (NCT05239728)

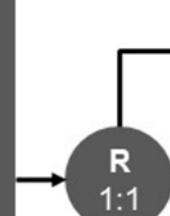
Key Eligibility Criteria

- Histologically confirmed ccRCC with no prior systemic therapy
- Surgery ≤ 12 weeks prior to randomization
- ECOG PS 0 or 1
- One of the following:
 - Intermediate-high risk of recurrence (M0):
 - pT2, grade 4 or sarcomatoid, N0
 - pT3, any grade, N0
 - High risk of recurrence (M0):
 - pT4, any grade, N0
 - Any pT, any grade, N+
- M1 NED

Stratification Factors

- Intermediate-high vs high vs M1 NED
- Tumor grade 1-2 vs 3-4

Median follow-up (data cutoff, Aug 23, 2025):
28.4 months (range, 15.0–40.1)



N = 921

Pembrolizumab 400 mg Q6W
for ~1 year (≤ 9 cycles)
+ **belzutifan 120 mg QD**
for ≤ 54 weeks

N = 920

Pembrolizumab 400 mg Q6W
for ~1 year (≤ 9 cycles)
+ **placebo QD**
for ≤ 54 weeks

Primary endpoint: DFS by investigator

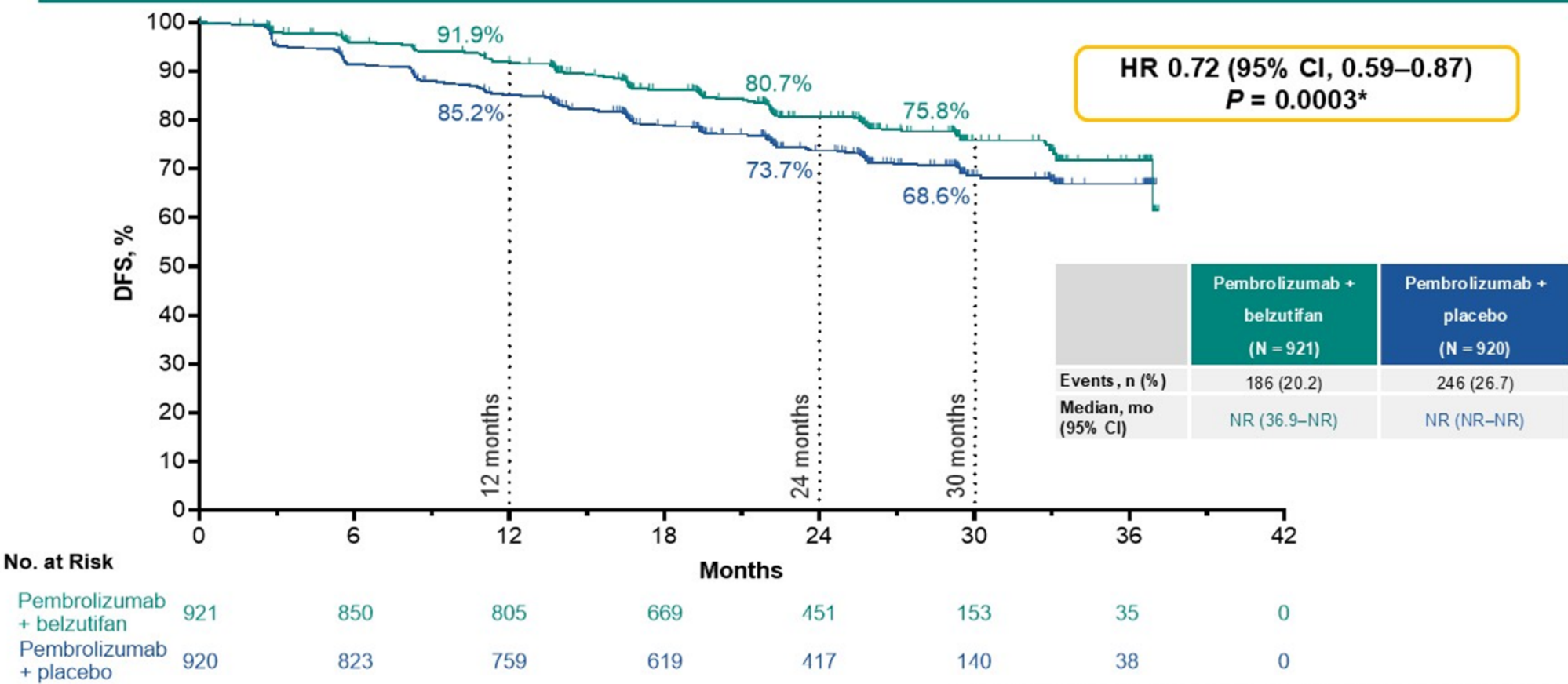
Key secondary endpoint: OS

Other secondary endpoints include: safety

NED, no evidence of disease; QD, daily; Q6W, every six weeks.

How to improve adjuvant pembrolizumab?

DFS by Investigator, ITT Population



Median follow-up: 28.4 months (range, 15.0–40.1).

*Denotes statistical significance by stratified log-rank test (p-value boundary, 0.01632).
NR, not reached. ITT population comprised all randomized participants. HRs and 95% CI estimated via stratified Cox proportional hazard model.
Data cutoff: August 23, 2025.

How to improve adjuvant pembrolizumab?

INTerpath-004 (NCT06307431) trial

Study design

Key Eligibility Criteria

- Histologically or cytologically confirmed RCC with clear cell or papillary histology with or without sarcomatoid features
- Intermediate–high-risk, high-risk, or M1 NED

Stratification Factors

- Histology (clear cell vs papillary)
- Disease risk (intermediate-high vs high vs M1 NED)

N ≈ 272
R (1:1)

n ≈ 136

V940 1 mg IM Q3W for 9 doses
+
Pembrolizumab 400 mg IV Q6W
for 9 cycles

n ≈ 136

Placebo Q3W for 9 doses
+
Pembrolizumab 400 mg IV Q6W
for 9 cycles

End Points

- **Primary:** DFS by investigator assessment
- **Secondary:** DMFS by investigator assessment, OS, safety

What about safety?

Summary of Safety Results, As-Treated Population

Participants, n (%)	Pembrolizumab + belzutifan ^{a,b} (N = 915)	Pembrolizumab + placebo ^{a,b} (N = 913)
Median duration on study therapy, mo (range)	12.4 (0.03–20.1)	12.4 (0.3–18.9)
Treatment-emergent AEs	905 (98.9)	863 (94.5)
Grade ≥3	477 (52.1)	276 (30.2)
Led to discontinuation of all study treatment	109 (11.9)	82 (9.0)
Led to death	10 (1.1)	11 (1.2)
Serious ^c	270 (29.5)	182 (19.9)
Serious ^c and led to discontinuation of all study treatment	59 (6.4)	43 (4.7)
Treatment-related AEs	884 (96.6)	737 (80.7)
Grade ≥3	386 (42.2)	163 (17.9)
Led to discontinuation of all study treatment	93 (10.2)	67 (7.3)
Led to death	3 (0.3)	3 (0.3)
Immune-mediated AEs or infusion reactions	324 (35.4)	353 (38.7)
Grade ≥3	86 (9.4)	76 (8.3)

What about safety?

Summary of Safety Results, As-Treated Population

Participants, n (%)	Pembrolizumab + belzutifan ^{a,b} (N = 915)	Pembrolizumab + placebo ^{a,b} (N = 913)
Median duration on study therapy, mo (range)	12.4 (0.03–20.1)	12.4 (0.3–18.9)
Treatment-emergent AEs	905 (98.9)	863 (94.5)
Grade ≥3	477 (52.1)	276 (30.2)
Led to discontinuation of all study treatment	109 (11.9)	82 (9.0)
Led to death	10 (1.1)	11 (1.2)
Serious ^c	270 (29.5)	182 (19.9)
Serious ^c and led to discontinuation of all study treatment	59 (6.4)	43 (4.7)
Treatment-related AEs	884 (96.6)	737 (80.7)
Grade ≥3	386 (42.2)	163 (17.9)
Led to discontinuation of all study treatment	93 (10.2)	67 (7.3)
Led to death	3 (0.3)	3 (0.3)
Immune-mediated AEs or infusion reactions	324 (35.4)	353 (38.7)
Grade ≥3	86 (9.4)	76 (8.3)

What about safety?

Summary of Safety Results, As-Treated Population

Participants, n (%)	Pembrolizumab + belzutifan ^{a,b} (N = 915)	Pembrolizumab + placebo ^{a,b} (N = 913)
Median duration on study therapy, mo (range)	12.4 (0.03–20.1)	12.4 (0.3–18.9)
Treatment-emergent AEs	905 (98.9)	863 (94.5)
Grade ≥3	477 (52.1)	276 (30.2)
Led to discontinuation of all study treatment	109 (11.9)	82 (9.0)
Led to death	10 (1.1)	11 (1.2)
Serious ^c	270 (29.5)	182 (19.9)
Serious ^c and led to discontinuation of all study treatment	59 (6.4)	43 (4.7)
Treatment-related AEs	884 (96.6)	737 (80.7)
Grade ≥3	386 (42.2)	163 (17.9)
Led to discontinuation of all study treatment	93 (10.2)	67 (7.3)
Led to death	3 (0.3)	3 (0.3)
Immune-mediated AEs or infusion reactions	324 (35.4)	353 (38.7)
Grade ≥3	86 (9.4)	76 (8.3)

How can we summarize the evidence face our RCC patient?

Parameter	Risk
Baseline risk of progression at 5y (KN564 criteria)	≈50%
Reduction of the risk of progression (relative)	29%
Absolute benefit at 5y (DFS)	9%
Reduction of the risk of death (relative)	34%
Absolute benefit at 5y (OS)	5%
Risk of high-grade toxicity (Tx-related)	<20%
Risk of TX-related death	0.3%
ADDING belzutifan to pembrolizumab vs. pembrolizumab	
Reduction of the risk of progression (relative)	28%
Risk of high-grade toxicity (Tx-related)	42% (+24%)