Renal Cell Carcinoma: Adjuvant Therapy



Daniel Heng MD MPH FRCPC

Clinical Professor and Head

Medical Oncology
Arthur J.E. Child Comprehensive Cancer Centre
University of Calgary

Chair, International mRCC Database Consortium (IMDC)

@DrDanielHeng

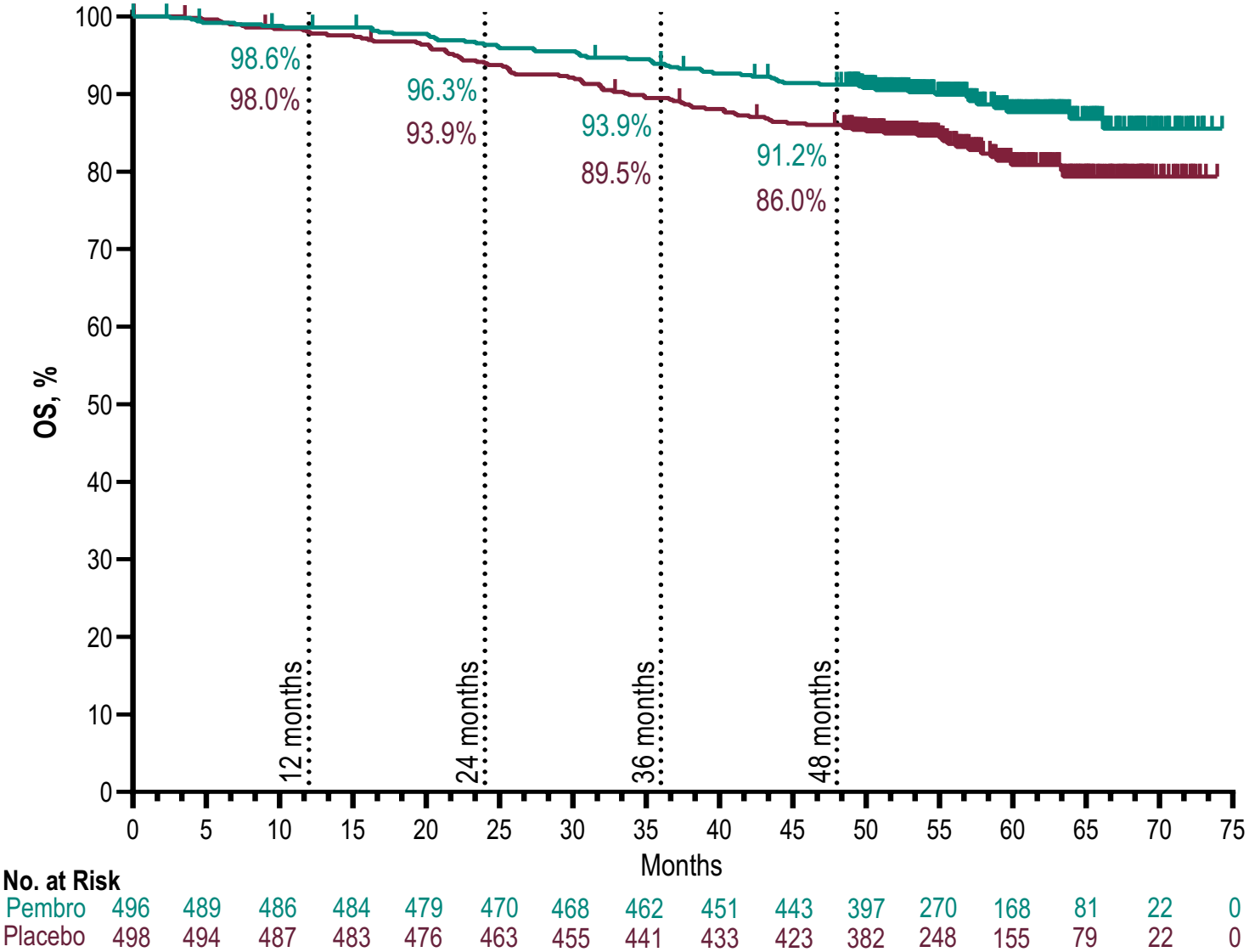
Arthur J.E Child Comprehensive Cancer Centre

imdc

Adjuvant Therapy

Int-High-M1NED Renal Cell Carcinoma

KEYNOTE 564 OS: Why we use Adjuvant Therapy



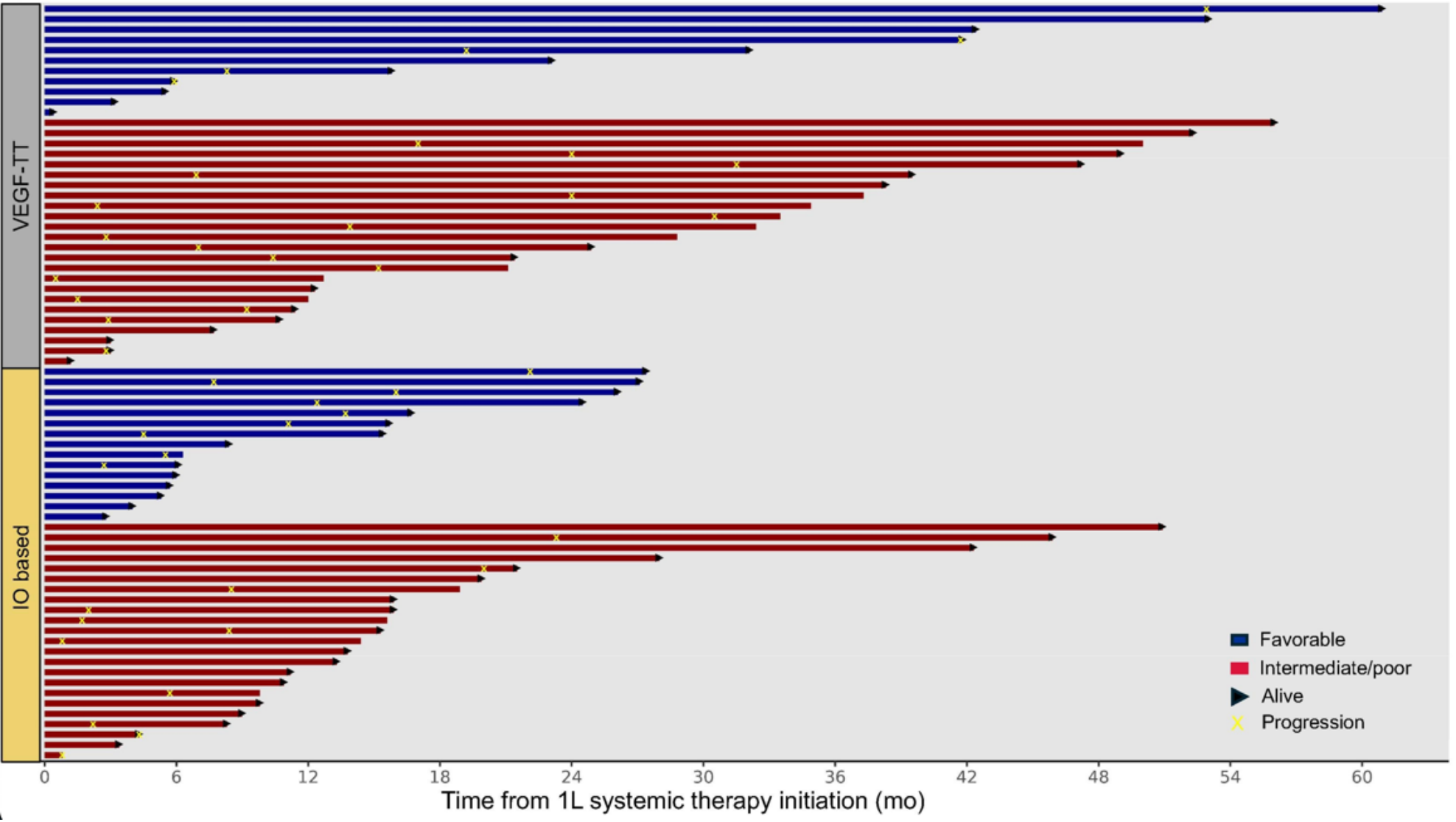
	Pembro (N = 496)	Placebo (N = 498)
Events, n	55	86
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)
Median follow-up was 57.2 months (range, 47.9–74.5)		

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.

Treatment Post Adjuvant Immunotherapy: Early Real World Evidence in 92 Patients

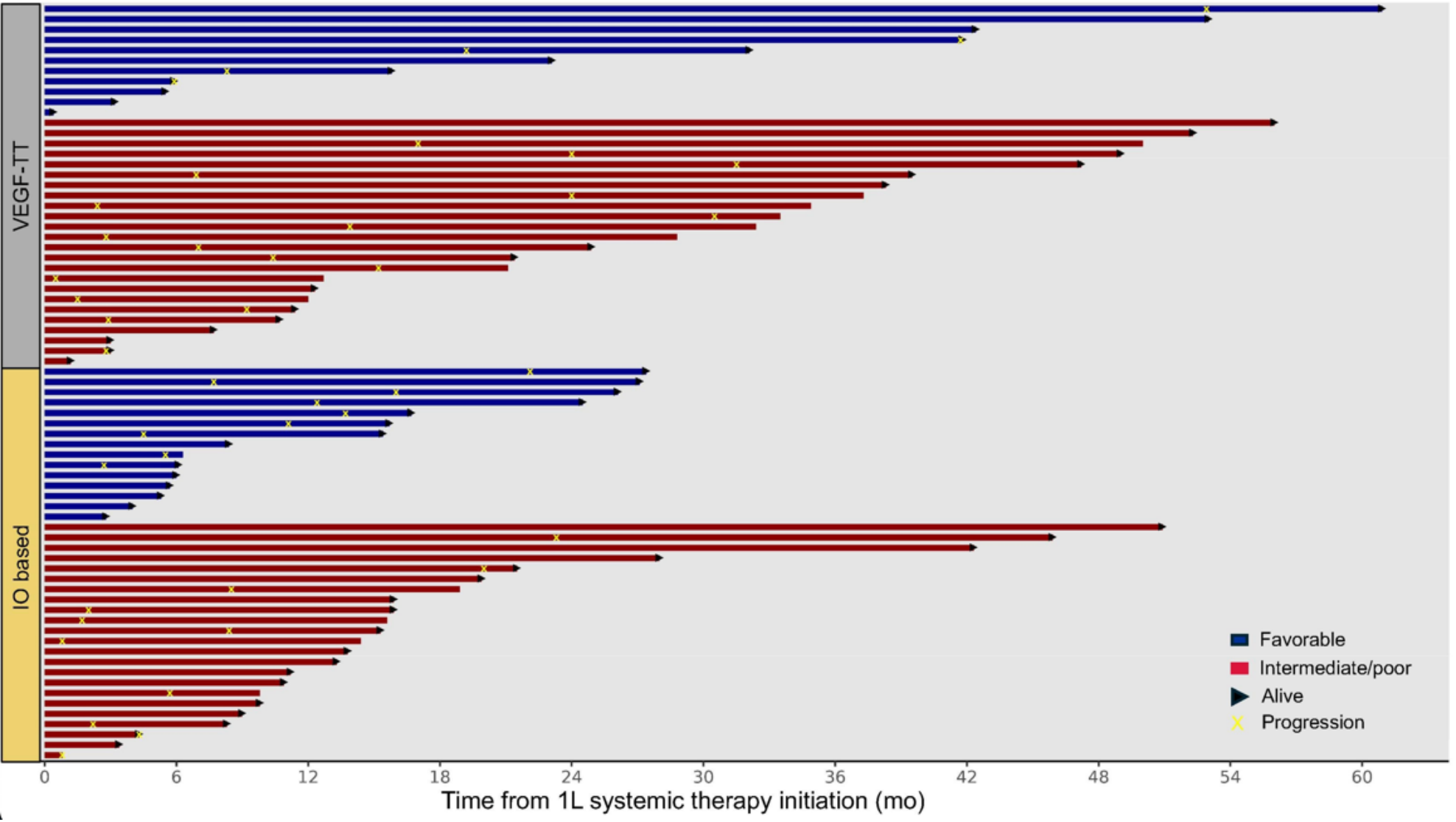


39% VEGF
28% VEGF IO
13% IO IO
20% Local Tx

More bone mets in relapse <3m

El-Zarif et al
Eur Urol 2024

Treatment Post Adjuvant Immunotherapy: Early Real World Evidence in 92 Patients

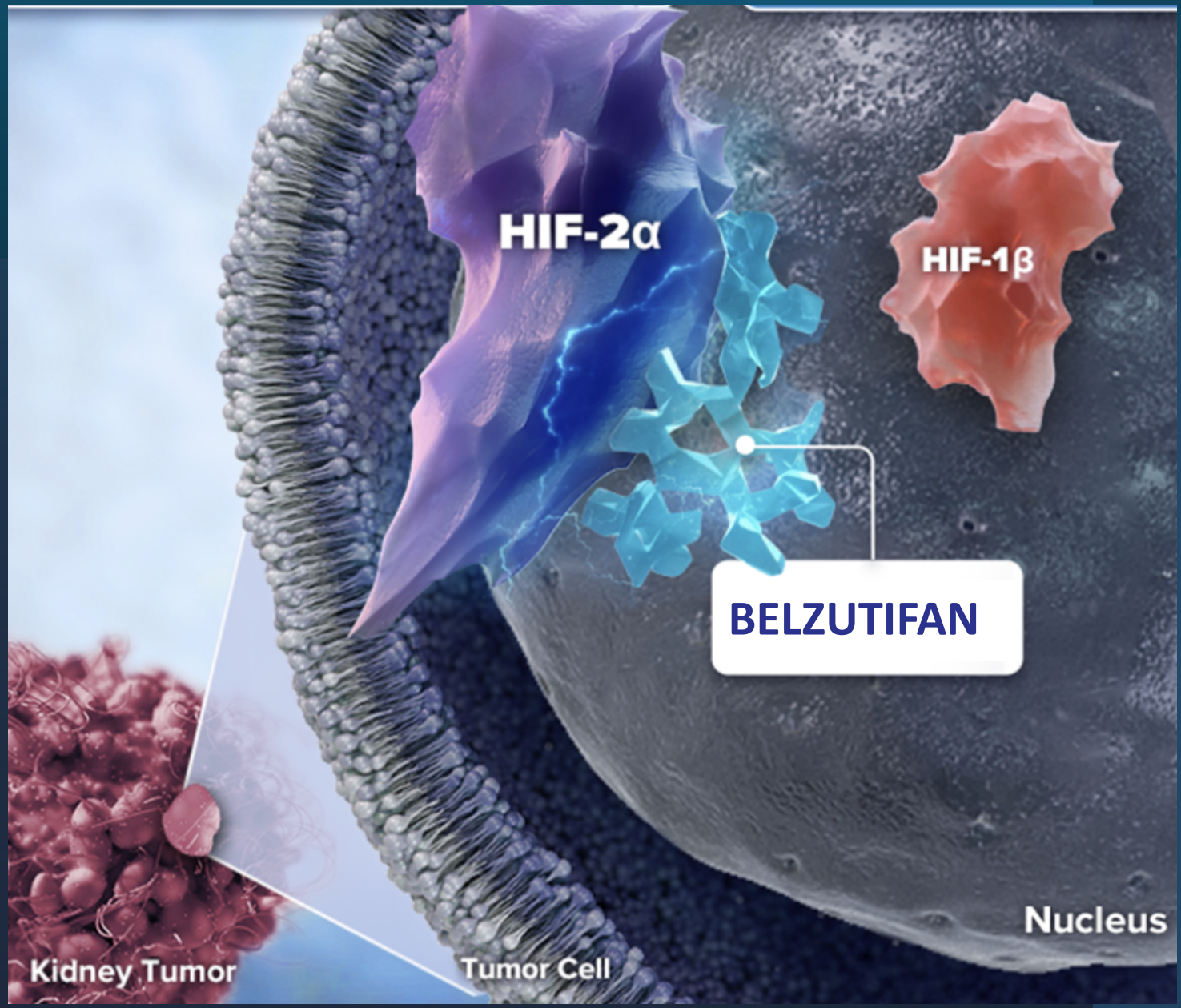


39% VEGF
28% VEGF IO
13% IO IO
20% Local Tx

More bone mets in relapse <3m

Are we changing the biology of relapse with adjuvant therapy?

El-Zarif et al
Eur Urol 2024



https://www.welireghcp.com/advanced-renal-cell-carcinoma/mechanism-of-action

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

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

R 1:1

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

Stratification Factors

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

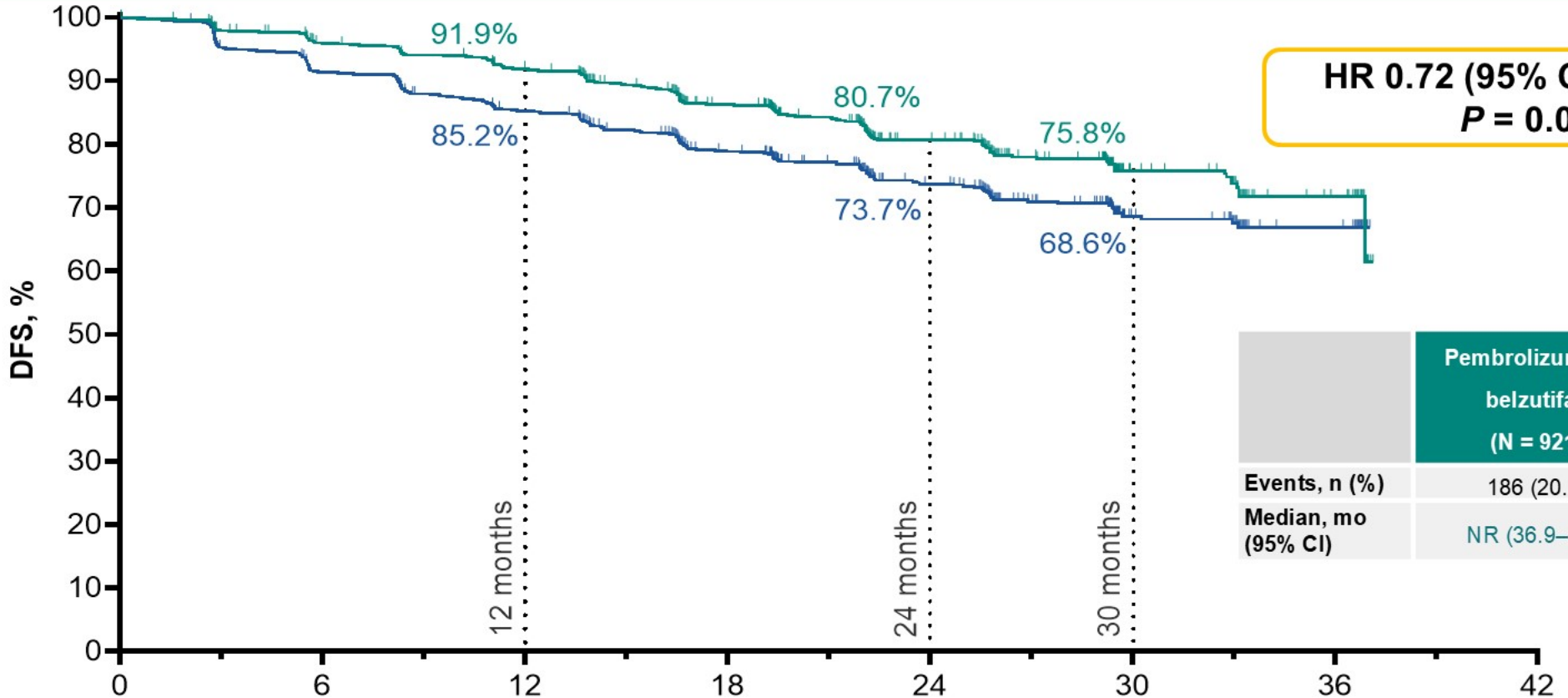
Primary endpoint: DFS by investigator
Key secondary endpoint: OS
Other secondary endpoints include: safety

This product is currently under evaluation by European health authorities and is not registered to date

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

Choueiri et al, ASCO GU 2026

DFS by Investigator, ITT Population



HR 0.72 (95% CI, 0.59–0.87)
P* = 0.0003

	Pembrolizumab + belzutifan (N = 921)	Pembrolizumab + placebo (N = 920)
Events, n (%)	186 (20.2)	246 (26.7)
Median, mo (95% CI)	NR (36.9–NR)	NR (NR–NR)

No. at Risk

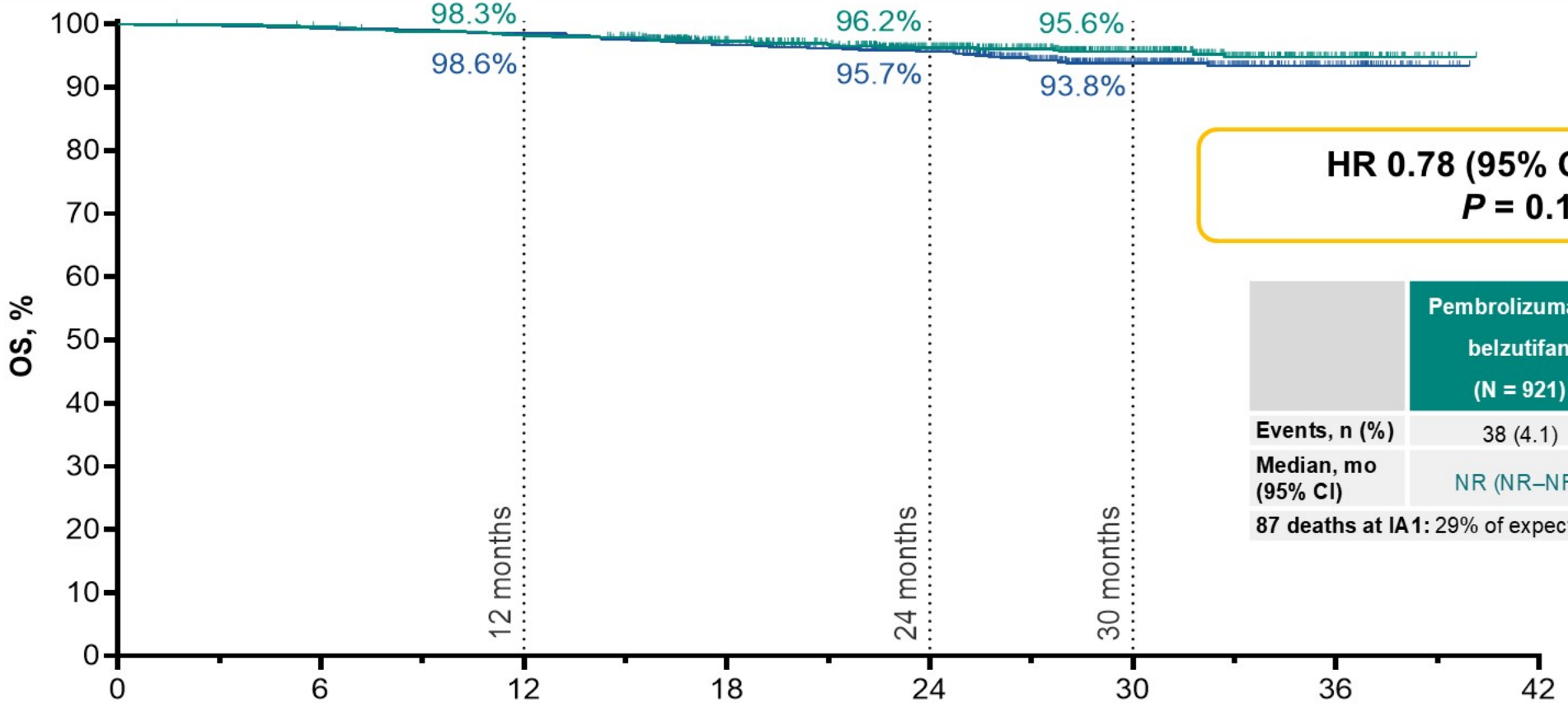
Pembrolizumab + belzutifan	921	850	805	669	451	153	35	0
Pembrolizumab + placebo	920	823	759	619	417	140	38	0

*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.

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

Choueiri et al, ASCO GU 2026

Interim OS Results, ITT Population



HR 0.78 (95% CI, 0.51–1.19)
P* = 0.1220

	Pembrolizumab + belzutifan (N = 921)	Pembrolizumab + placebo (N = 920)
Events, n (%)	38 (4.1)	49 (5.3)
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)

87 deaths at IA1: 29% of expected events at final analysis

No. at Risk

Pembrolizumab + belzutifan	921	914	900	805	631	319	70	0
Pembrolizumab + placebo	920	914	907	807	638	319	69	0

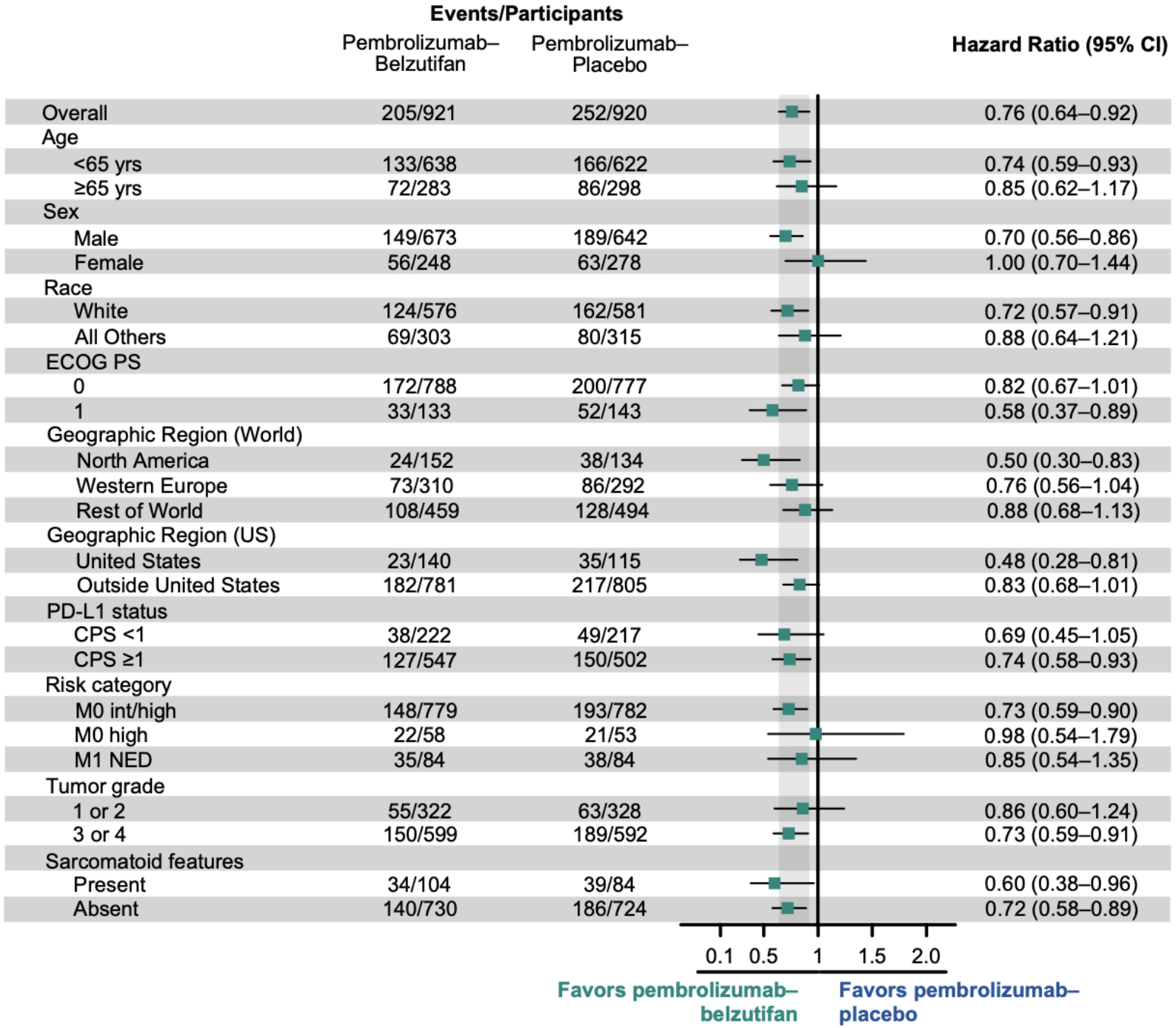
*Did not reach statistical significance by stratified log-rank test (p-value boundary, 0.00003).
Final analysis for OS to occur after approximately 300 OS events. HRs and 95% CI estimated via stratified Cox proportional hazard model.

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

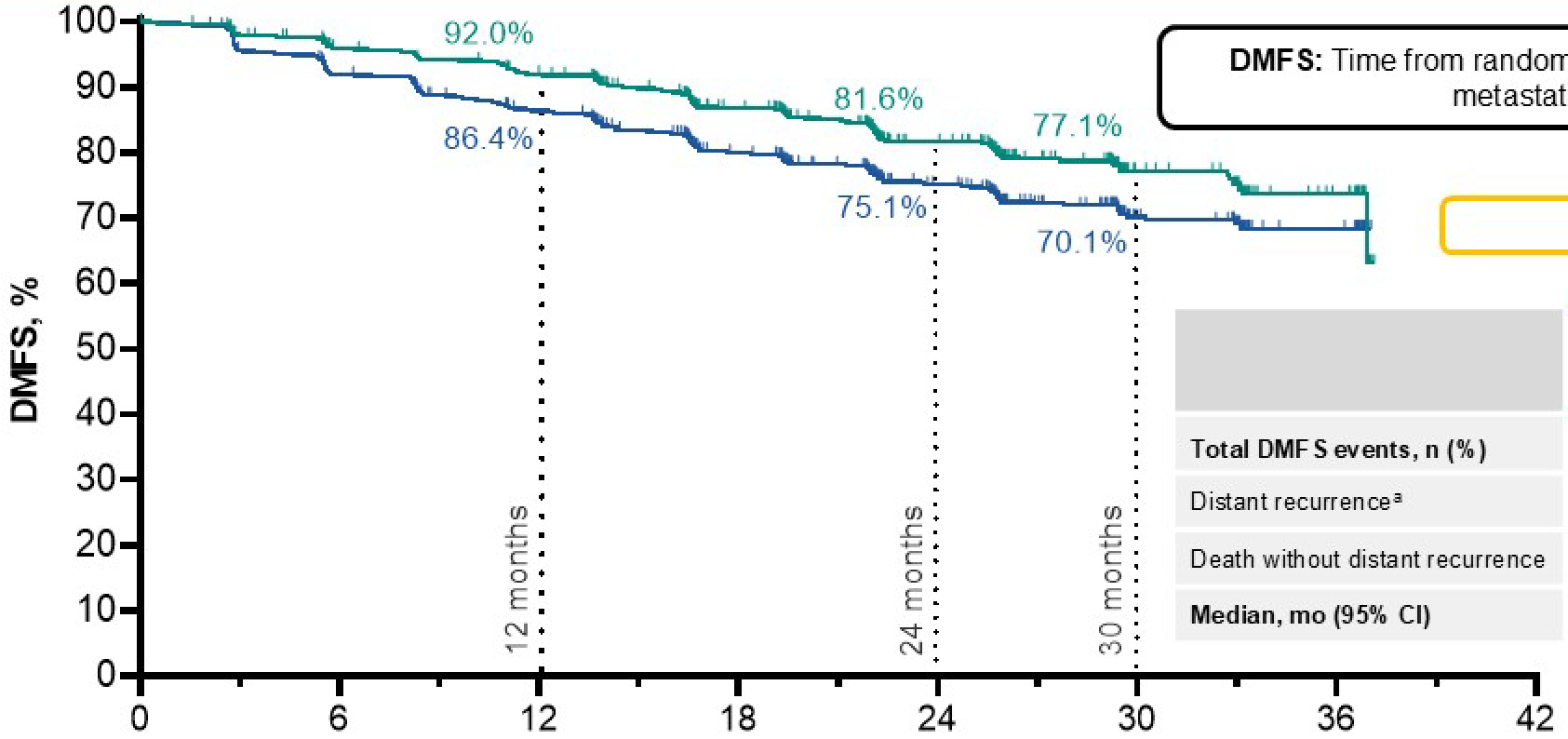
Choueiri et al, ASCO GU 2026

Data cutoff: August 23, 2025.

DFS
BICR


Events/Participants
Pembrolizumab–Belzutifan
Pembrolizumab–Placebo
Hazard Ratio (95% CI)
Overall 205/921 252/920 0.76 (0.64–0.92)
Age
<65 yrs 133/638 166/622 0.74 (0.59–0.93)
≥65 yrs 72/283 86/298 0.85 (0.62–1.17)
Sex
Male 149/673 189/642 0.70 (0.56–0.86)
Female 56/248 63/278 1.00 (0.70–1.44)
Race
White 124/576 162/581 0.72 (0.57–0.91)
All Others 69/303 80/315 0.88 (0.64–1.21)
ECOG PS
0 172/788 200/777 0.82 (0.67–1.01)
1 33/133 52/143 0.58 (0.37–0.89)
Geographic Region (World)
North America 24/152 38/134 0.50 (0.30–0.83)
Western Europe 73/310 86/292 0.76 (0.56–1.04)
Rest of World 108/459 128/494 0.88 (0.68–1.13)
Geographic Region (US)
United States 23/140 35/115 0.48 (0.28–0.81)
Outside United States 182/781 217/805 0.83 (0.68–1.01)
PD-L1 status
CPS <1 38/222 49/217 0.69 (0.45–1.05)
CPS ≥1 127/547 150/502 0.74 (0.58–0.93)
Risk category
M0 int/high 148/779 193/782 0.73 (0.59–0.90)
M0 high 22/58 21/53 0.98 (0.54–1.79)
M1 NED 35/84 38/84 0.85 (0.54–1.35)
Tumor grade
1 or 2 55/322 63/328 0.86 (0.60–1.24)
3 or 4 150/599 189/592 0.73 (0.59–0.91)
Sarcomatoid features
Present 34/104 39/84 0.60 (0.38–0.96)
Absent 140/730 186/724 0.72 (0.58–0.89)
0.1 0.5 1 1.5 2.0
Favors pembrolizumab–belzutifan
Favors pembrolizumab–placebo

Distant Metastasis-free Survival, ITT Population



DMFS: Time from randomization to first documented distant metastatic lesion or death

HR 0.71 (0.59–0.87)

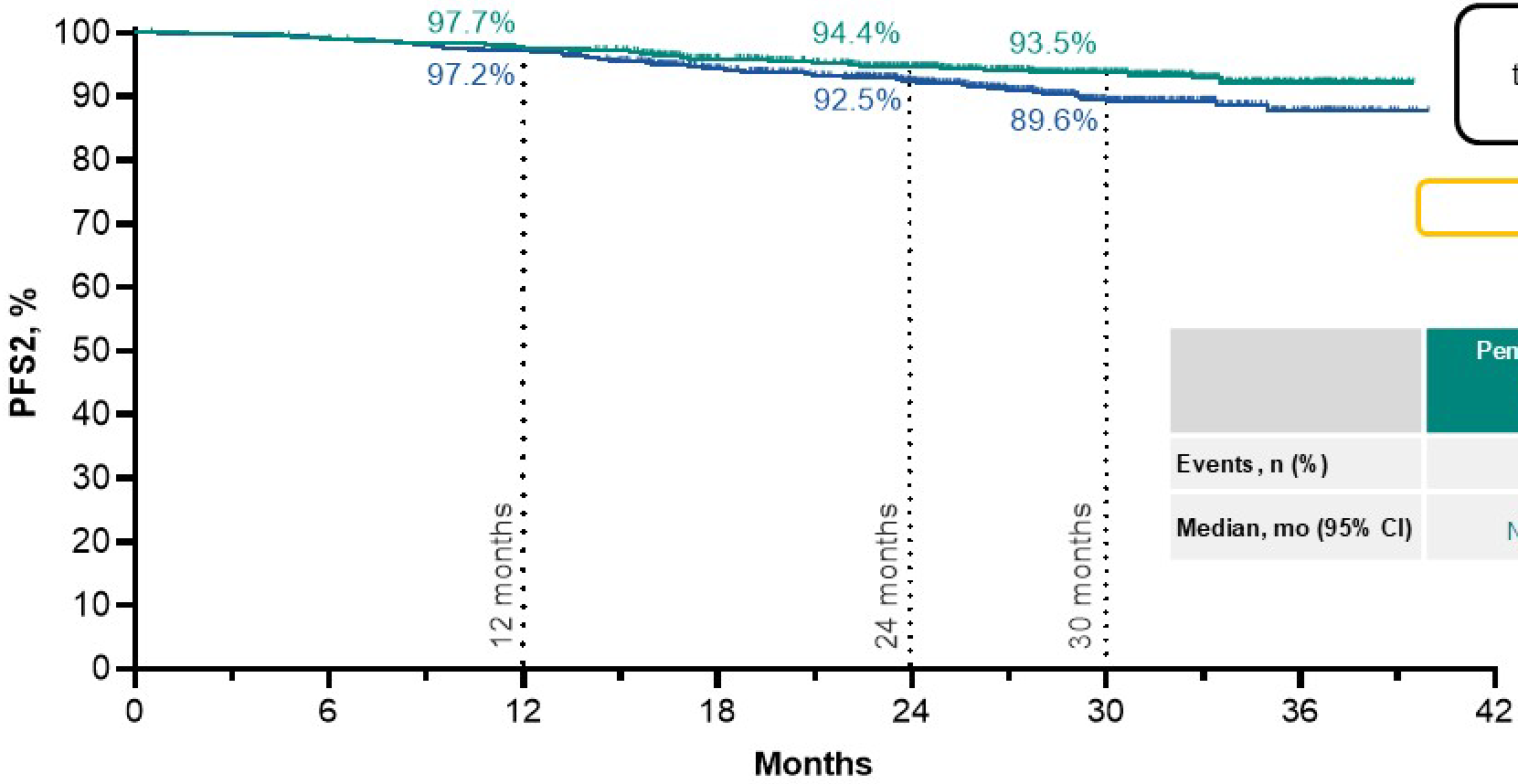
	Pembrolizumab + belzutifan (N = 921)	Pembrolizumab + placebo (N = 920)
Total DMFS events, n (%)	**175 (19.0)**	**232 (25.2)**
Distant recurrence[a]	158 (17.2)	207 (22.5)
Death without distant recurrence	17 (1.8)	25 (2.7)
Median, mo (95% CI)	NR (36.9–NR)	NR (NR–NR)

No. at Risk

Pembrolizumab + belzutifan	921	850	806	671	452	153	35	0
Pembrolizumab + placebo	920	823	760	619	417	140	38	0

[a]Local recurrence was reported in 13 (1.4%) pts in the pembrolizumab + belzutifan arm vs 14 (1.5%) in the pembrolizumab + placebo arm.
HRs and 95% CI estimated via stratified Cox proportional hazard model.
Data cutoff: August 23, 2025.

Progression-free Survival 2, ITT Population



PFS2: time from randomization to progression on next-line therapy or any-cause death

HR 0.68 (0.48–0.94)

	Pembrolizumab + belzutifan (N = 921)	Pembrolizumab + placebo (N = 920)
Events, n (%)	57 (6.2)	84 (9.1)
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)

No. at Risk

Pembrolizumab + belzutifan	921	909	895	791	620	311	67	0
Pembrolizumab + placebo	920	911	894	788	620	308	67	0

HRs and 95% CI estimated via stratified Cox proportional hazard model.
Data cutoff: August 23, 2025.

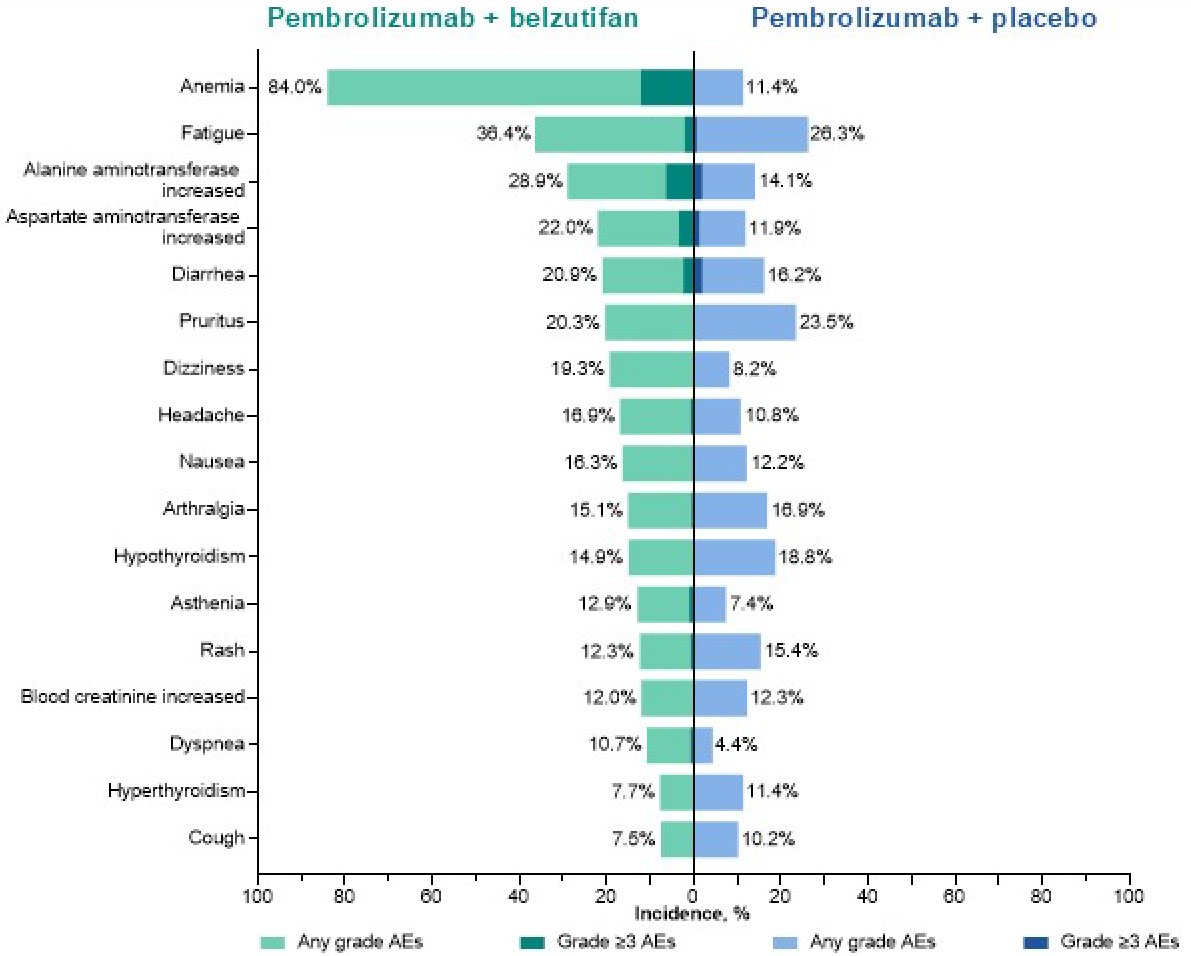
Subsequent Therapies in Participants with Recurrence

Participants, n (%)	Participants with Documented Recurrence	
	Pembrolizumab + belzutifan (N = 171)	Pembrolizumab + placebo (N = 221)
Received any subsequent therapy[a]	137 (80.1)	184 (83.3)
Received systemic anticancer drug therapy	105 (61.4)	141 (63.8)
VEGF/VEGFR inhibitor	88 (51.5)	135 (61.1)
Immune checkpoint inhibitor[b]	53 (31.0)	46 (20.8)
Others[c]	18 (10.5)	26 (11.8)
Received radiation	27 (15.8)	42 (19.0)
Received surgery	34 (19.9)	46 (20.8)

[a]Participants could have multiple subsequent anticancer therapies for RCC or a combination of drug therapy/radiation/surgery; each participant is counted once in each applicable category. [b]Included anti-PD-(L)1 and anti-CTLA-4 therapy. [c]Included but was not limited to everolimus (5.8% with pembrolizumab + belzutifan vs 6.8% with pembrolizumab + placebo) and belzutifan (1.2% vs 1.8%, respectively).
Data cutoff: August 23, 2025.

Summary of Safety, 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)



[a]Median number of pembrolizumab cycles was 9 (range 1–9) for both arms. [b]Median dose intensity (range) was 107.3 mg/day (8.3–120.0) for belzutifan (89.4% of planned starting dose) and 119.5 mg/day (54.1–141.2) for placebo (99.6% of planned starting dose). [c]Serious adverse events were defined as any adverse event that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was judged by the investigator to be a serious adverse event.
Safety was assessed in all participants who received ≥1 dose of study treatment.
Data cutoff: August 23, 2025.

Summary and Management of Anemia[a], As-Treated Population

Participants, n (%)	Pembrolizumab + belzutifan (N = 915)	Pembrolizumab + placebo (N = 913)
TEAEs of anemia[a]	771 (84.3)	107 (11.7)
Grade ≥3	111 (12.1)	5 (0.5)
Led to interruption of belzutifan/placebo	226 (24.7)	6 (0.7)
Led to dose reduction of belzutifan/placebo	158 (17.3)	0
Led to discontinuation of belzutifan/placebo	37 (4.0)	1 (0.1)
Supportive therapy for anemia		
Treated with blood transfusions only	41 (4.5)	6 (0.7)
Treated with ESA only	65 (7.1)	2 (0.2)
Treated with ESA and blood transfusions	10 (1.1)	0 (0.0)

[a]Includes participants with anemia and decreased hemoglobin.
ESA, erythropoiesis-stimulating agent.
Data cutoff: August 23, 2025.

Implications of LITESPARK 022

- Addition of belzutifan improves DFS, now FDA approved
- Patient selection
  - Do we use this in everyone, do we use this in high risk, do we use it in the healthy, do we wait for overall survival benefit?
  - Could biomarkers help us?
    - ctDNA not sensitive enough currently
    - KIM 1 under evaluation
- If we use belzutifan in the adjuvant setting can we use it in the metastatic setting?

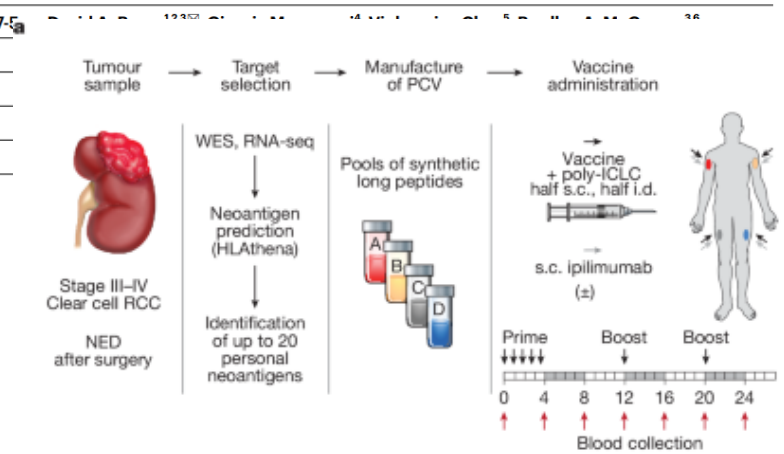
Personalized Vaccines in RCC

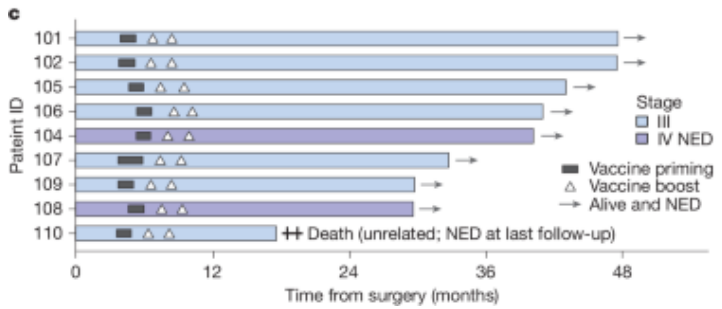
Article

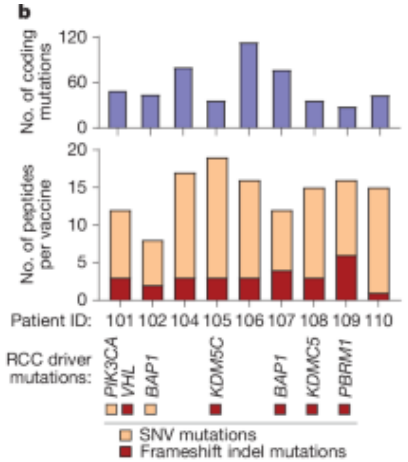
A neoantigen vaccine generates antitumour immunity in renal cell carcinoma

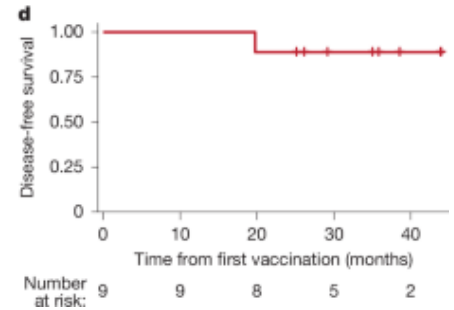
https://doi.org/10.1038/s41586-024-08507-5
Received: 19 February 2024
Accepted: 10 December 2024
Published online: 05 February 2025
Open access
Check for updates

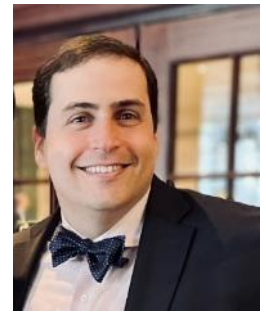
- Personalized cancer vaccine
- Creates anticancer immune response
- Median of 34.7 months, 9/9 pts remained cancer-free







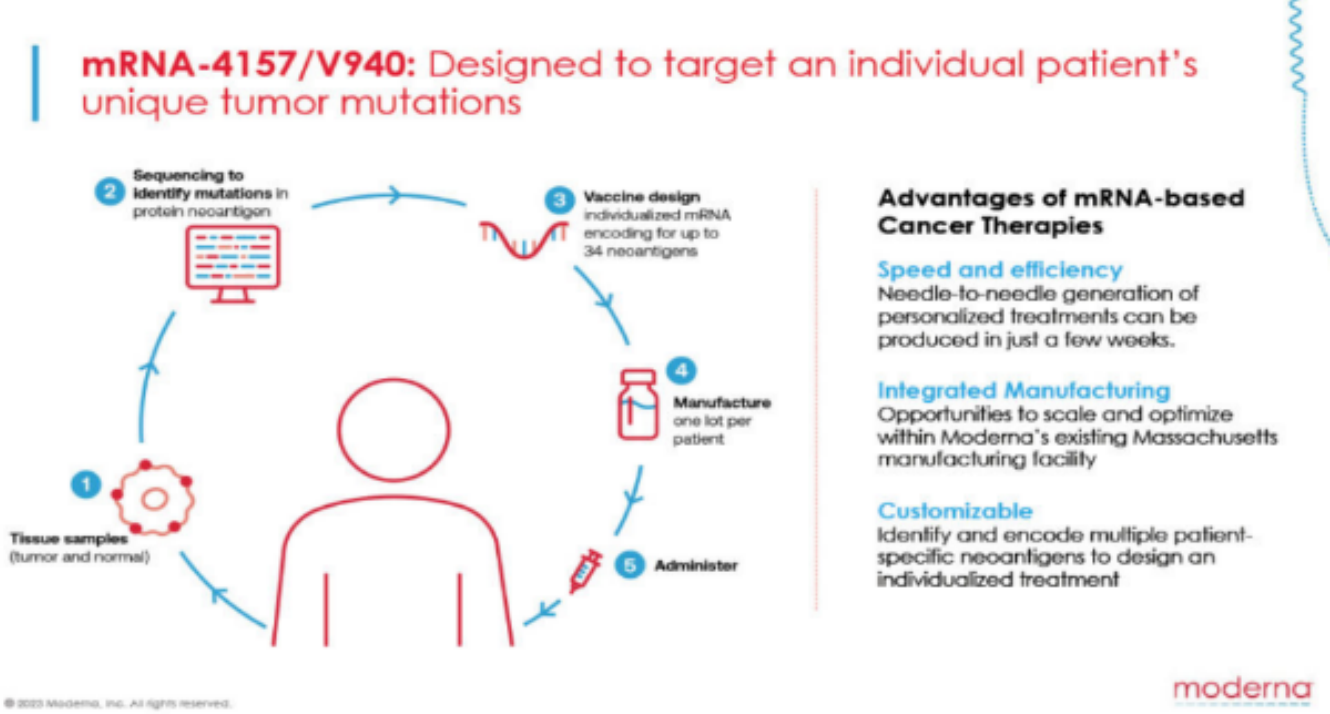








Personalized Vaccines
V940-004
INTerpath-004



Key Inclusion Criteria (N≈272)

- clear cell or papillary RCC
- Intermediate-high-risk, high-risk, or M1 NED RCC :
  - Intermediate-high-risk RCC: pT2 Gr4, N0, M0; pT3 Gr3/4, N0, M0
  - High-risk RCC: pT4, N0, M0; pT any stage, N1, M0
  - M1 NED RCC (≤2 years from nephrectomy)

R

V940 (mRNA-4157) IM Q3W (up to 9 doses) + Pembrolizumab 400 mg IV Q6W (up to 9 doses; up to ~54 weeks)

Placebo IM Q3W (up to 9 doses) + Pembrolizumab 400 mg IV Q6W (up to 9 doses; up to ~54 weeks)

Primary Endpoints	Secondary Endpoints
▪ DFS	▪ OS, DMFS, Safety

Study Details | NCT06307431 | A Study of Adjuvant Intismeran Autogene (V940) and Pembrolizumab in Renal Cell Carcinoma (V940-004). | ClinicalTrials.gov

Conclusions

- Adjuvant therapy is evolving and patient selection remains an art
- More personalized approaches to come

@DrDanielHeng
daniel.heng@cancercarealberta.ca



