Second Opinion: Optimal Management of Localized Renal Cell Carcinoma

Part 1 of a 2-Part CME Satellite Symposium Series Held in Conjunction with the 2026 American Urological Association Annual Meeting (AUA2026)

Sunday, May 17, 2026

8:00 AM – 9:30 AM ET

Faculty

Eric A Singer, MD, MA, MS, FACS, FASCO
Ulka Vaishampayan, MD

Moderator

Thomas E Hutson, DO, PharmD, PhD

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Faculty

Eric A Singer, MD, MA, MS, FACS, FASCO
The Dave Longaberger Endowed Chair in Urology
Professor of Urology and Bioethics
Chief, Division of Urologic Oncology
Director, Urologic Oncology Fellowship
The Ohio State University Comprehensive Cancer Center
Columbus, Ohio

Moderator

Thomas E Hutson, DO, PharmD, PhD
Medical Oncology — Clinical Research
Drug Development
Texas Oncology
GU Executive and Bridge Committees
Sarah Cannon Research Institute (SCRI)
Abilene, Texas

Ulka Vaishampayan, MD
Beverly Mitchell Research Professor of Oncology
Co-Leader of Translational Clinical Research Program
University of Michigan/Rogel Cancer Center
Ann Arbor, Michigan

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Dr Singer — Disclosures
Faculty

No relevant financial relationships to disclose.

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Dr Vaishampayan — Disclosures
Faculty

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Consulting Agreements	Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Exelixis Inc, Janssen Biotech Inc, Kowa Pharmaceuticals America, Merck, Novartis
Contracted Research	Merck
Nonrelevant Financial Relationships	SWOG

Dr Hutson — Disclosures
Moderator

No relevant financial relationships to disclose.

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Dr Armstrong — Disclosures
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Dr McKay — Disclosures
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Dr Motzer — Disclosures
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Contracted Research	Bristol Myers Squibb, Eisai Inc, Exelixis Inc, Merck

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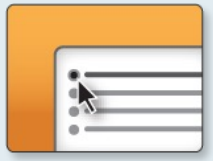
Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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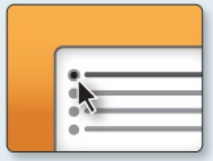
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program. An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Second Opinion: Investigators Provide Perspectives on the Current and Future Management of Prostate Cancer

Part 2 of a 2-Part CME Satellite Symposium Series Held in Conjunction with the 2026 American Urological Association Annual Meeting (AUA2026)

Sunday, May 17, 2026

5:30 PM – 7:30 PM ET

Faculty

Neeraj Agarwal, MD, FASCO
Daniel P Petrylak, MD
Fred Saad, CQ, MD
Neal D Shore, MD

Moderator

Elisabeth I Heath, MD

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Second Opinion: Optimal Management of Localized Renal Cell Carcinoma

Part 1 of a 2-Part CME Satellite Symposium Series Held in Conjunction with the 2026 American Urological Association Annual Meeting (AUA2026)

Sunday, May 17, 2026

8:00 AM – 9:30 AM ET

Faculty

Eric A Singer, MD, MA, MS, FACS, FASCO
Ulka Vaishampayan, MD

Moderator

Thomas E Hutson, DO, PharmD, PhD

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Second Opinion

Andrew J Armstrong, MD, ScM
Professor of Medicine, Urology, Pharmacology and Cancer Biology
Director of Research
Duke Cancer Institute Center for Prostate and Urologic Cancers
Division of Medical Oncology
Departments of Medicine and Urology
Duke University
Durham, North Carolina

Rana R McKay, MD, FASCO
Professor of Medicine, Urology, and Radiation Medicine and Applied Sciences
Associate Director, Clinical Research
Co-Lead, Genitourinary Program
Moores Cancer Center
University of California San Diego
San Diego, California

Robert J Motzer, MD
Attending Physician, Department of Medicine
Jack and Dorothy Byrne Chair in Clinical Oncology
Memorial Sloan Kettering Cancer Center
New York, New York

Sandy Srinivas, MD
Professor of Oncology
Clinical Research Leader, GU Oncology
Stanford University
Stanford, California

Neil Love, MD
Research To Practice
Miami, Florida

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Agenda

Module 1: Current Indications for Adjuvant Immune Checkpoint Inhibitor Therapy in the Management of Renal Cell Carcinoma (RCC) — Dr Singer

Module 2: Potential Role of Hypoxia-Inducible Factor-2 Alpha (HIF-2α) Inhibitors as a Component of Adjuvant Treatment — Dr Hutson

Module 3: Tolerability of Current and Emerging Adjuvant Approaches for RCC — Dr Vaishampayan

Agenda

Module 1: Current Indications for Adjuvant Immune Checkpoint Inhibitor Therapy in the Management of Renal Cell Carcinoma (RCC) — Dr Singer

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Module 3: Tolerability of Current and Emerging Adjuvant Approaches for RCC — Dr Vaishampayan

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Indications for Adjuvant Immune Checkpoint Inhibitor Therapy in Renal Cell Carcinoma

Eric A. Singer, MD, MA, MS, FACS, FASCO
The Dave Longaberger Endowed Chair in Urology
Professor of Urology and Bioethics
Chief, Division of Urologic Oncology
Director, Urologic Oncology Fellowship
The Ohio State University Comprehensive Cancer Center

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Learning Objectives

- Review available RCC risk stratification schema
- Discuss current indications for adjuvant immunotherapy
- Consider future directions

Scope

- NOT metastatic disease
- NOT focused on biomarkers
- NOT focused on active surveillance
- NOT able to cover every stratification system/update

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Why is Risk Stratification Needed?

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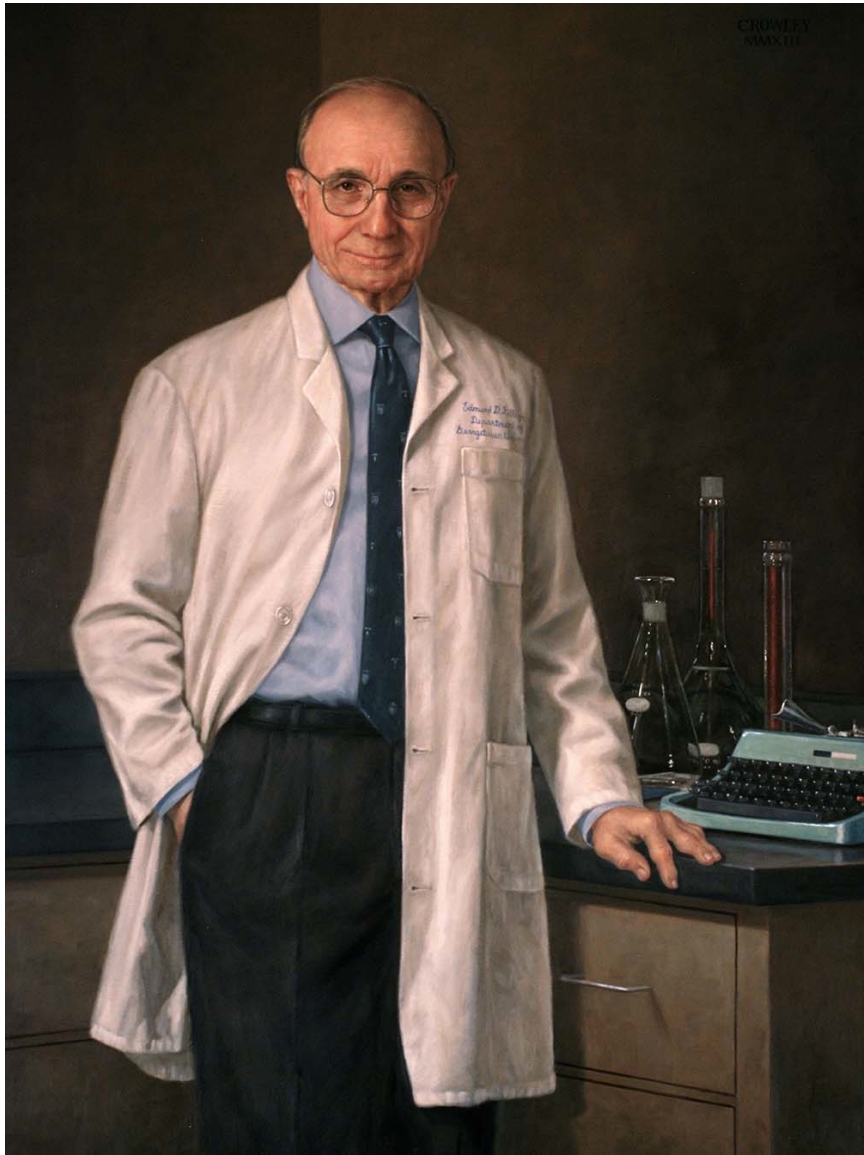
Why is Risk Stratification Needed?

"Diagnostic elegance and therapeutic parsimony"



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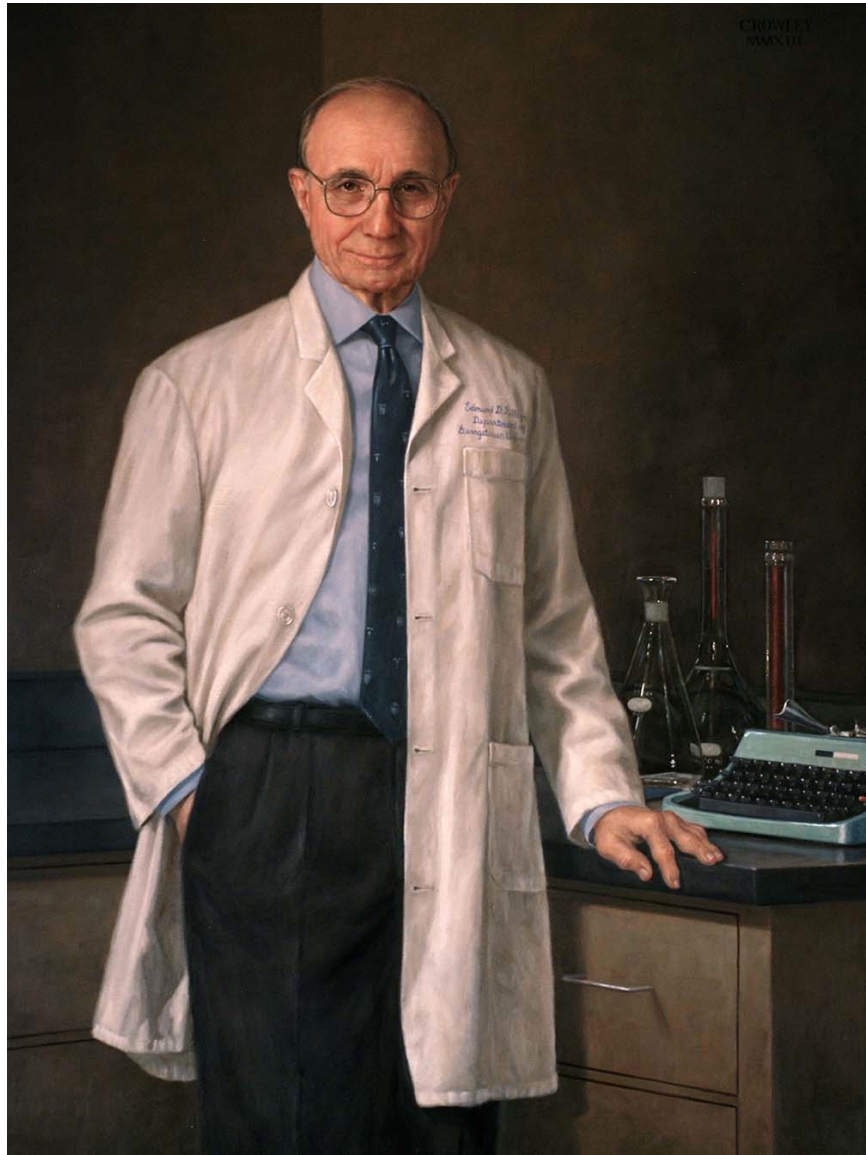
Why is Risk Stratification Needed?

"*Diagnostic elegance* and therapeutic parsimony"

- Incidentally found
- Symptomatic



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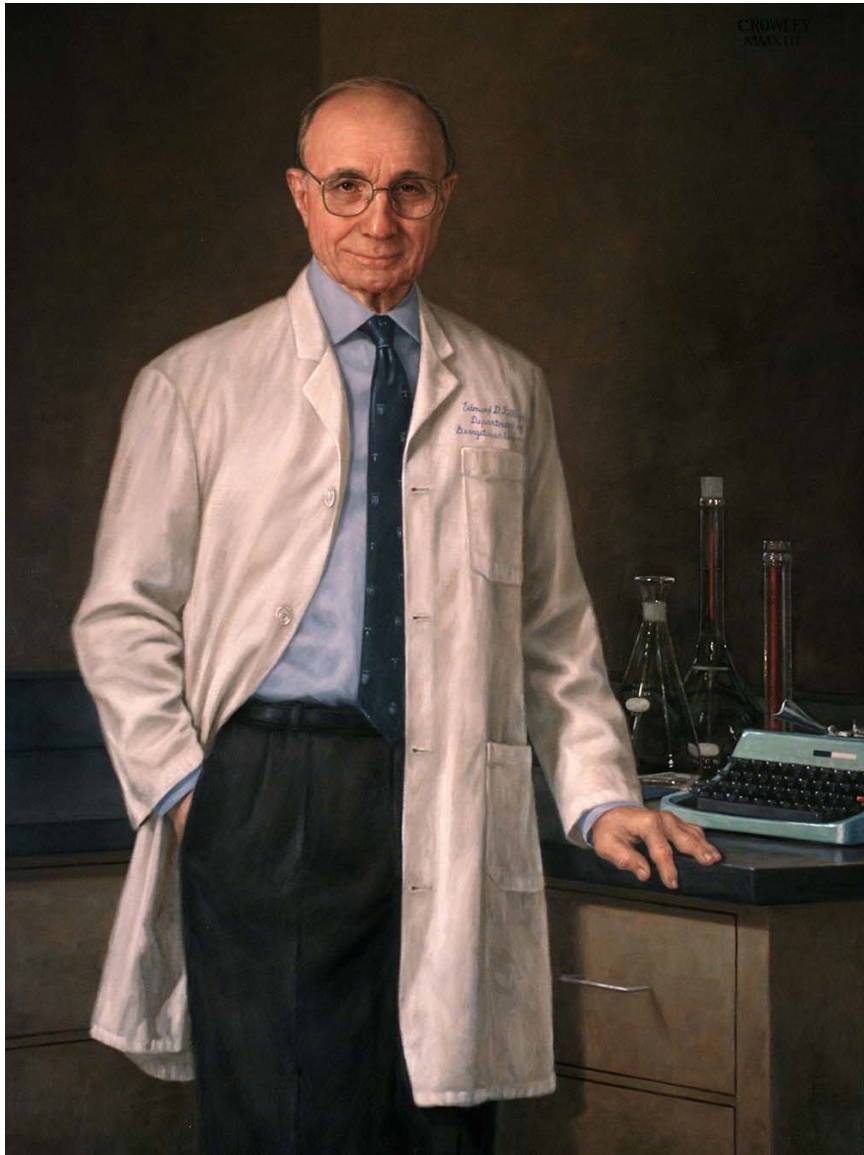
Why is Risk Stratification Needed?

"Diagnostic elegance and *therapeutic parsimony*"

- Surveillance
- Biopsy
- Ablation (thermal, histotripsy)
- Radiation
- Resection (partial vs. total)
- Adjuvant therapy (IO, IO+HIF, trial)



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Improved Prognostication of Renal Cell Carcinoma Using an Integrated Staging System

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By Amnon Zisman, Allan J. Pantuck, Fredrick Dorey, Jonathan W. Said, Oleg Shvarts, Deanna Quintana, Barbara J. Gitlitz, Jean B. deKernion, Robert A. Figlin, and Arie S. Belldegrun

Journal of Clinical Oncology, Vol 19, No 6 (March 15), 2001: pp 1649-1657

UISS	1997 TNM Stage	Furman's Grade	ECOG	2-Year Survival		5-Year Survival	
				%	SE	%	SE
I	I	1, 2	0	96	2.5	94	2.5
II	I	1, 2	1 or more	89	3.8	67	6.4
	I	3, 4	Any				
	II	Any	Any				
	III	Any	0				
	III	1	1 or more				
III	III	2-4	1 or more	66	6.5	39	2.8
	IV	1, 2	0				
IV	IV	3, 4	0	42	3.5	23	3.1
		1-3	1 or more				
V	IV	4	1 or more	9	6.2	0	4.0

Abbreviation: TNM, tumor-node-metastasis.

0022-5347/01/1661-0063/0
THE JOURNAL OF UROLOGY®

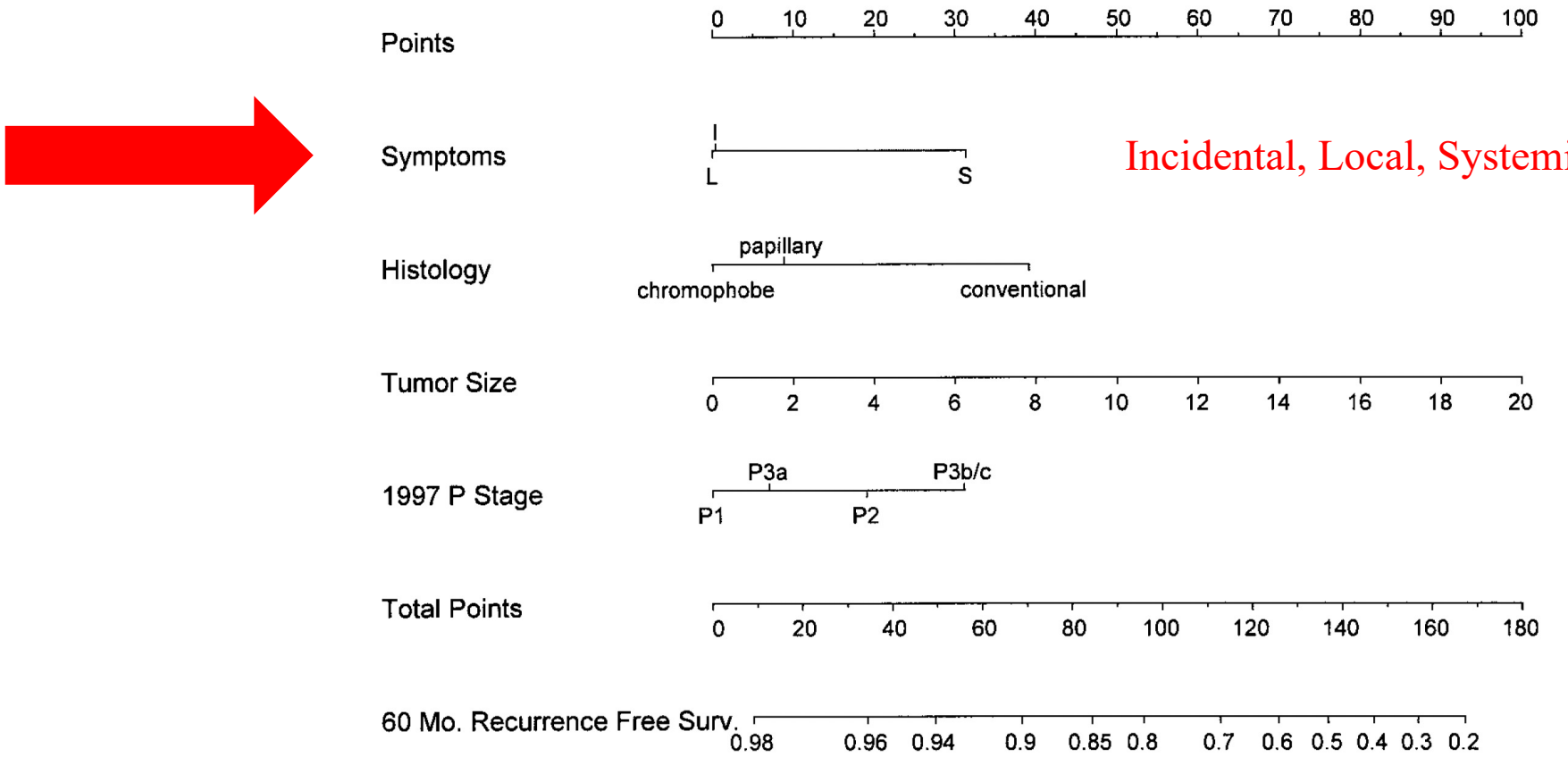
Vol. 166, 63–67, July 2001
Printed in U.S.A.

A POSTOPERATIVE PROGNOSTIC NOMOGRAM FOR RENAL CELL CARCINOMA

MICHAEL W. KATTAN,* VICTOR REUTER, ROBERT J. MOTZER, JARED KATZ AND PAUL RUSSO

From the Departments of Urology, Epidemiology and Biostatistics, Pathology, and Medicine (Genitourinary Oncology Service), Memorial Sloan-Kettering Cancer Center, New York, New York

POSTOPERATIVE PROGNOSTIC NOMOGRAM FOR RENAL CELL CARCINOMA



0022-5347/02/1686-2395/0
The Journal of Urology®

Vol. 168, 2395–2400, December 2002
Printed in U.S.A.
DOI: 10.1097/01.ju.0000035885.91935.d5

AN OUTCOME PREDICTION MODEL FOR PATIENTS WITH CLEAR CELL RENAL CELL CARCINOMA TREATED WITH RADICAL NEPHRECTOMY BASED ON TUMOR STAGE, SIZE, GRADE AND NECROSIS: THE SSIGN SCORE

IGOR FRANK, MICHAEL L. BLUTE, JOHN C. CHEVILLE, CHRISTINE M. LOHSE, AMY L. WEAVER AND HORST ZINCKE

TNM

Size

Grade

Necrosis

TABLE 5. *SSIGN score algorithm*
The scores in this table are added together and the total is used to determine survival using table 6.

Feature	Score
T stage:	
pT1	0
pT2	1
pT3a	2
pT3b	2
pT3c	2
pT4	0
N stage:	
pNx	0
pN0	0
pN1	2
pN2	2
M stage:	
pM0	0
pM1	4
Tumor size (cm.):	
Less than 5	0
5 or Greater	2
Nuclear grade:	
1	0
2	0
3	1
4	3
Necrosis:	
Absent	0
Present	2

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Multi-Institutional Validation of a New Renal Cancer–Specific Survival Nomogram

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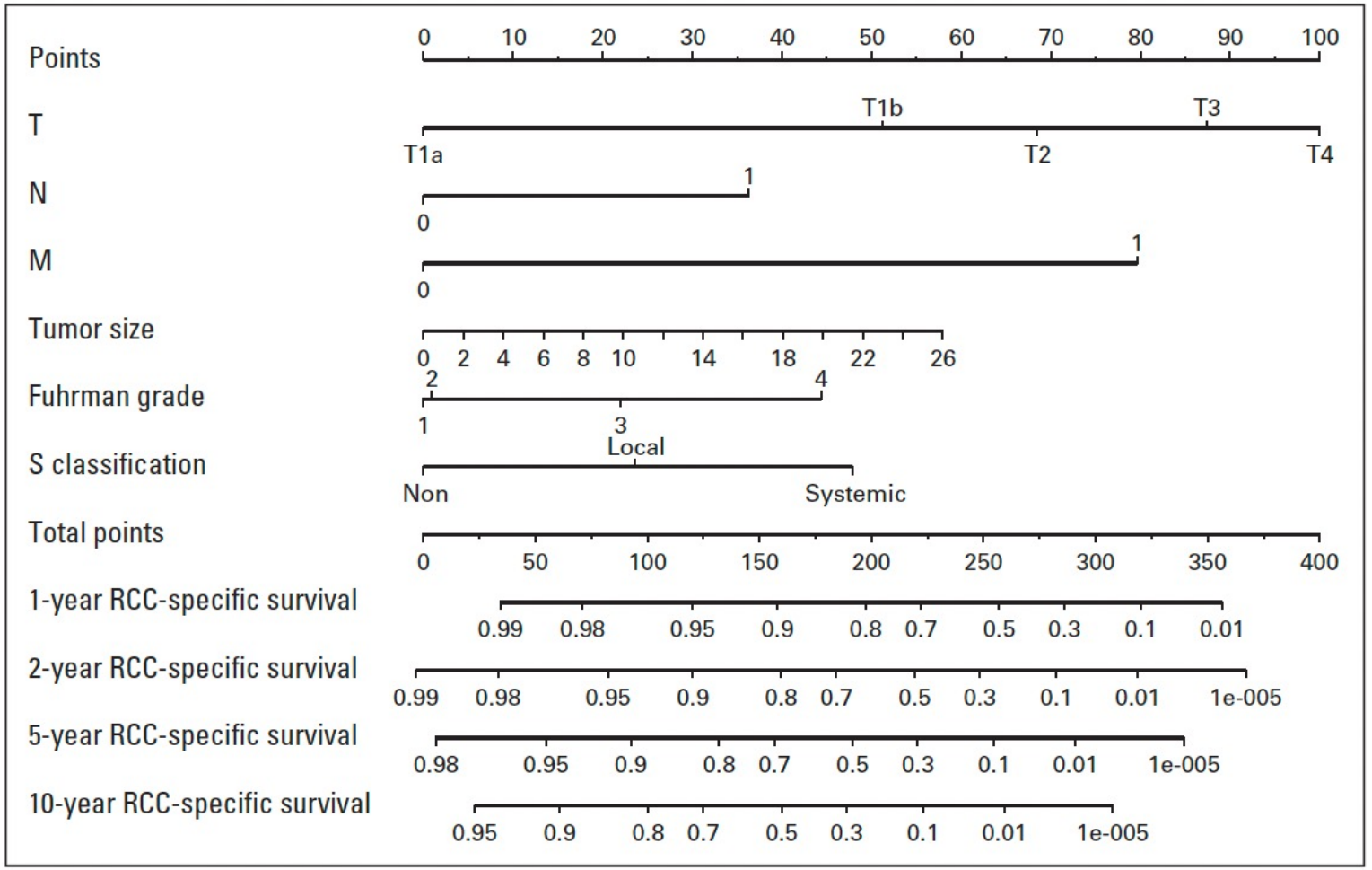
Pierre I. Karakiewicz, Alberto Briganti, Felix K.-H. Chun, Quoc-Dien Trinh, Paul Perrotte, Vincenzo Ficarra, Luca Cindolo, Alexandre De La Taille, Jacques Tostain, Peter F.A. Mulders, Laurent Salomon, Richard Zigeuner, Tommaso Prayer-Galetti, Denis Chautard, Antoine Valeri, Eric Lechevallier, Jean-Luc Descotes, Herve Lang, Arnaud Mejean, and Jean-Jacques Patard

VOLUME 25 · NUMBER 11 · APRIL 10 2007

JOURNAL OF CLINICAL ONCOLOGY



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Multi-Institutional Validation of a New Renal Cancer–Specific Survival Nomogram

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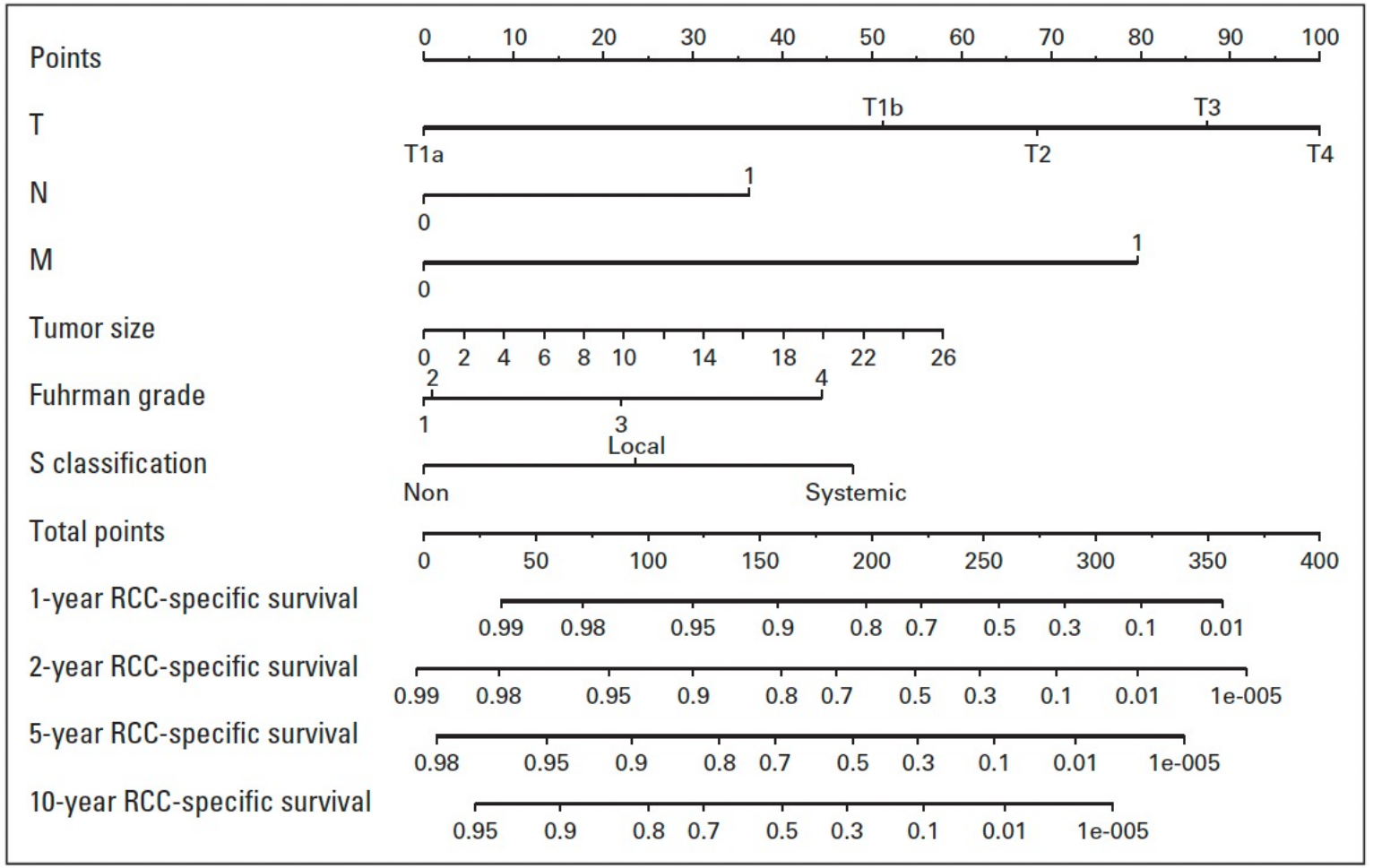
VOLUME 25 · NUMBER 11 · APRIL 10 2007
JOURNAL OF CLINICAL ONCOLOGY

- **Larger test and validation sets**
- **Improved prediction 2.5-5.4%**
- **Longer predictive timespan**
- **Readily obtained data elements (not necrosis)**



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Predicting Disease Recurrence, Early Progression, and Overall Survival Following Surgical Resection for High-risk Localized and Locally Advanced Renal Cell Carcinoma

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Andres F. Correa[a,*], *Opeyemi A. Jegede*[b], *Naomi B. Haas*[c], *Keith T. Flaherty*[d], *Michael R. Pins*[e], *Adebowale Adeniran*[f], *Edward M. Messing*[g], *Judith Manola*[b], *Christopher G. Wood*[h], *Christopher J. Kane*[i], *Michael A.S. Jewett*[j], *Janice P. Dutcher*[k], *Robert S. DiPaola*[l], *Michael A. Carducci*[m], *Robert G. Uzzo*[a]

EUROPEAN UROLOGY 80 (2021) 20–31

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Predicting Disease Recurrence, Early Progression, and Overall Survival Following Surgical Resection for High-risk Localized and Locally Advanced Renal Cell Carcinoma

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Andres F. Correa [a,], Opeyemi A. Jegede [b], Naomi B. Haas [c], Keith T. Flaherty [d], Michael R. Pins [e], Adebowale Adeniran [f], Edward M. Messing [g], Judith Manola [b], Christopher G. Wood [h], Christopher J. Kane [i], Michael A.S. Jewett [j], Janice P. Dutcher [k], Robert S. DiPaola [l], Michael A. Carducci [m], Robert G. Uzzo [a]*

EUROPEAN UROLOGY 80 (2021) 20–31

- Study population consists of 1,735 patients recruited and followed in the ECOG-ACRIN 2805 (ASSURE) RCC trial
- Adjuvant targeted therapy (sunitinib and sorafenib) in patients with fully resected intermediate- and high-risk localized kidney cancer (**pT1b and G3–4; pT2/pT3/pT4; N1**)

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Predicting Disease Recurrence, Early Progression, and Overall Survival Following Surgical Resection for High-risk Localized and Locally Advanced Renal Cell Carcinoma

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Andres F. Correa[a,*], *Opeyemi A. Jegede*[b], *Naomi B. Haas*[c], *Keith T. Flaherty*[d], *Michael R. Pins*[e], *Adebowale Adeniran*[f], *Edward M. Messing*[g], *Judith Manola*[b], *Christopher G. Wood*[h], *Christopher J. Kane*[i], *Michael A.S. Jewett*[j], *Janice P. Dutcher*[k], *Robert S. DiPaola*[l], *Michael A. Carducci*[m], *Robert G. Uzzo*[a]

EUROPEAN UROLOGY 80 (2021) 20–31

A

Risk Factors	DFS Points	OS Points
Vascular Invasion, ref = Intra/renal/IVC vs None	1.0	NA
Age at RCC Diagnosis (years), ref = ≤ 51.0		
>51.0 ≤ 60.0	NA	1.0
> 60.0		2.0
¥Renal Histology, ref = Chromophobe or Pap. Type 1		
Clear Cell (CC), Papillary Type II, Mixed Papillary, or variant histology >25% CC	4.5	4.0
Unclassified or < 25% CC	5.5	4.5
Tumor Size (cm), ref = ≤7.0		
>7.0 ≤10.0	1.5	1.5
>10.0	2.5	2.0
Fuhrman Grade, Grade 4 vs Grade 1-3	2.0	2.0
Coagulative Necrosis, Yes vs No	1.5	1.5
Regional Lymph Nodes (pN), pN1/2 vs pN0/X	3.0	2.5

B

Risk Group	Disease Free Survival Estimate (%)			
	1-year	2-year	5-year	10-year
Low Risk (0-5.5 points)	98.1	92.6	82.6	69.3
Intermediate risk (6-8 points)	89.7	76.2	61.1	42.3
High Risk (≥8.5 points)	68.9	49.2	33.1	25.3

C

Risk Group	Overall Survival Estimate (%)			
	1-year	2-year	5-year	10-year
Low Risk (0-4.5 points)	100.0	100.0	98.4	91.4
Favorable Intermediate risk (5-7 points)	99.1	97.2	87.7	72.3
Unfavorable Intermediate risk (7.5-9.5 points)	96.5	90.7	73.8	52.6
High Risk (≥10 points)	85.5	70.6	49.0	36.3

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EUROPEAN UROLOGY 80 (2021) 20–31

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Cancer Prediction Tools

‹ Back to Home

Assure RCC Prognostic Nomogram

A post-operative prediction model which provides a comprehensive review of expected oncological outcomes in patients with renal cell carcinoma.

Nomogram Details

N (number of pts in study)	1735
Area under the curve (AUC) or C index (CI)	0.68
Externally validated	No
Journal name	European Urology
Journal Impact factor	17.581
Year of publication	2021

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Renal Mass and Localized Renal Cancer: Evaluation, Management, and Follow-up: AUA Guideline: Part II

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Steven C. Campbell,* Robert G. Uzzo, Jose A. Karam, Sam S. Chang, Peter E. Clark and Lesley Souter

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THE JOURNAL OF UROLOGY®
https://doi.org/10.1097/JU.0000000000001912
Vol. 206, 209-218, August 2021

1. Patients who have been managed with surgery (PN or RN) for a malignant renal mass should be classified into one of the following risk groups for surveillance:

Low Risk (LR):	**pT1 and Grade 1/2**
Intermediate Risk (IR):	**pT1 and Grade 3/4 or pT2 any Grade**
High Risk (HR):	**pT3 any Grade**
Very High Risk (VHR):	**pT4 or pN1, or sarcomatoid/rhabdoid dedifferentiation, or macroscopic positive margin**

If final microscopic surgical margins are positive for cancer, the risk category should be considered at least one level higher, and increased clinical vigilance should be exercised.

Adjuvant Therapy for Renal Cell Carcinoma: End Points, Outcomes, and Risk Assessments

JCO Precis Oncol 7:e2200407. © 2023

Joseph J. Boyle, BS[1]; John L. Pfail, MD[1]; Benjamin J. Lichtbroun, MD[1]; and Eric A. Singer, MD, MA, MS[1,2]

TABLE 1. Adjuvant TKI Clinical Trials

Trial	No.	Treatment Regimen	Time	Primary End Point	Outcome	Notes
ASSURE	1,943	*Sorafenib* or *sunitinib* *v* placebo	1 year	DFS	No significant difference. *Sunitinib*: 5.8 years HR, 1.02; 97.5% CI, 0.85 to 1.23; *P* = .8038 *Sorafenib*: 6.1 years HR, 0.97; 97.5% CI, 0.80 to 1.17; *P* = .7184 Placebo: 6.6 years	Dose reduction of sunitinib and sorafenib midtrial because of higher-than-expected rates of discontinuation
S-TRAC	615	*Sunitinib* *v* placebo	1 year	DFS	Significant difference. *Sunitinib*: 6.8 years HR, 0.76; 95% CI, 0.59 to 0.98; *P* = .03 Placebo: 5.6 years	Led to FDA approval of sunitinib in the adjuvant setting for RCC
PROTECT	1,538	*Pazopanib* *v* placebo	1 year	DFS	No significant difference HR, 0.86; 95% CI, 0.70 to 1.06; *P* = .165	Dose reduction of pazopanib midtrial because of higher-than-expected rates of discontinuation
ATLAS	724	*Axitinib* *v* placebo	3 years	DFS	No significant difference HR, 0.870; 95% CI, 0.660 to 1.147; *P* = .3211	Terminated early because of lack of response at interim analysis
SORCE	1,711	*Sorafenib* *v* placebo	3 years	DFS	No significant difference HR, 1.01; 95% CI, 0.83 to 1.23; *P* = .95	Greater than 50% of patients stopped treatment early because of adverse events
EVEREST	1,218	*Everolimus* *v* placebo	Nine cycles of 6 weeks	DFS	No significant difference at interim analysis HR, 0.85; 95% CI, 0.72 to 1.00; *P* = .0246	Subgroup analysis showed significant improvement in DFS among patients at very high risk of recurrence

Abbreviations: DFS, disease-free survival; FDA, US Food and Drug Administration; HR, hazard ratio; RCC, renal cell carcinoma.

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Adjuvant Therapy for Renal Cell Carcinoma: End Points, Outcomes, and Risk Assessments

JCO Precis Oncol 7:e2200407. © 2023

Joseph J. Boyle, BS[1]; John L. Pfail, MD[1]; Benjamin J. Lichtbroun, MD[1]; and Eric A. Singer, MD, MA, MS[1,2]

TABLE 1. Adjuvant TKI Clinical Trials

Trial	No.	Treatment Regimen	Time	Primary End Point	Outcome	Notes
ASSURE	1,943	*Sorafenib* or *sunitinib* *v* placebo	1 year	DFS	No significant difference. *Sunitinib*: 5.8 years HR, 1.02; 97.5% CI, 0.85 to 1.23; *P* = .8038 *Sorafenib*: 6.1 years HR, 0.97; 97.5% CI, 0.80 to 1.17; *P* = .7184 Placebo: 6.6 years	Dose reduction of sunitinib and sorafenib midtrial because of higher-than-expected rates of discontinuation
S-TRAC	615	*Sunitinib* *v* placebo	1 year	DFS	Significant difference. *Sunitinib*: 6.8 years HR, 0.76; 95% CI, 0.59 to 0.98; *P* = .03 Placebo: 5.6 years	Led to FDA approval of sunitinib in the adjuvant setting for RCC
PROTECT	1,538	*Pazopanib* *v* placebo	1 year	DFS	No significant difference HR, 0.86; 95% CI, 0.70 to 1.06; *P* = .165	Dose reduction of pazopanib midtrial because of higher-than-expected rates of discontinuation
ATLAS	724	*Axitinib* *v* placebo	3 years	DFS	No significant difference HR, 0.870; 95% CI, 0.660 to 1.147; *P* = .3211	Terminated early because of lack of response at interim analysis
SORCE	1,711	*Sorafenib* *v* placebo	3 years	DFS	No significant difference HR, 1.01; 95% CI, 0.83 to 1.23; *P* = .95	Greater than 50% of patients stopped treatment early because of adverse events
EVEREST	1,218	*Everolimus* *v* placebo	Nine cycles of 6 weeks	DFS	No significant difference at interim analysis HR, 0.85; 95% CI, 0.72 to 1.00; *P* = .0246	Subgroup analysis showed significant improvement in DFS among patients at very high risk of recurrence

Abbreviations: DFS, disease-free survival; FDA, US Food and Drug Administration; HR, hazard ratio; RCC, renal cell carcinoma.

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Perioperative systemic therapy in high-risk renal cell carcinoma following nephrectomy: a narrative review

Transl Cancer Res 2024;13(11):6511-6528

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Adam Khorasanchi[1]^, Taylor Goodstein[2], Shawn Dason[2], Eric A. Singer[2], Danielle Zimmerman[1], Yuanquan Yang[1,3]^

Table 3 Summary of adjuvant targeted therapy trials in high-risk RCC

Trial	N	Agent	Duration of adjuvant tx	Primary outcome	Result	Tx discontinuation rate due to AEs
ASSURE (84)	1,943	Sunitinib, sorafenib	1 yr	DFS	Not significant	Sunitinib (20%), sorafenib (20%)
S-TRAC (86)	615	Sunitinib	1 yr	DFS	Significant	28%
PROTECT (87)	1,538	Pazopanib	1 yr	DFS	Not significant	800 mg dose (39%), 600 mg dose (35%)
ARISER (88)	864	Girentuximab	24 wks	DFS, OS	Not significant	2%
ATLAS (89)	724	Axitinib	1 yr minimum	DFS	Not significant	19%
SORCE (90)	1,711	Sorafenib	1 yr, 3 yr	DFS	Not significant	30% (1 yr), 34% (3 yrs)
EVEREST (91)	1,545	Everolimus	54 wks	DFS	Not significant	37%

RCC, renal cell carcinoma; tx, treatment; AE, adverse event; yr, year; DFS, disease-free survival; wks, weeks; OS, overall survival.

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Table 4 Adjuvant immunotherapy trials in high-risk RCC

Trial	KEYNOTE-564 (19,94)	IMmotion010 (28)	CheckMate-914 (27)	PROSPER (99)
Treatment	Pembrolizumab, placebo	Atezolizumab, placebo	Nivolumab + ipilimumab, placebo	Nivolumab, observation
Mechanism of action	Anti-PD-1	Anti-PD-L1	Anti-PD-1 and anti-CTLA4	Anti-PD-1
Primary endpoint met?	Yes, DFS	No, DFS	No, DFS	No, RFS
DFS/RFS (mo), HR (95% CI), P value	NR *vs.* NR, 0.68 (0.53–0.87), P=0.002	57.2 *vs.* 49.5, 0.93 (0.75–1.15), P=0.5	NR *vs.* 50.7, 0.92 (0.71–1.19), P=0.53	0.97 (0.74–1.28), P=0.43
Treatment duration (mo)	12	12	6	10 (including neoadjuvant and adjuvant)
Median follow-up (mo)	30	44.7	37	n/a
Histology included	Clear cell	Clear cell (93%) or non-clear cell with sarcomatoid features	Clear cell	Clear cell (83%) or non-clear cell
Risk stratification (% enrolled): stage, grade included	Intermediate-high risk (74%): pT2, G4; pT3, G any; high-risk (20%): pT4, G any, pTxN+, G any	Intermediate-high risk (65%): pT2, G4; pT3a, G3–4; high-risk (21%): pT3b–T4, G any, pTxN+, G any	Intermediate-high risk (56%): pT2a, G3–4; pT2b, G any; pT3, G1–2; high-risk (43%): pT3, G3–4; pT4, G any; pTxN+, G any	High-risk: cT2, G4; cT3–4, G any; cTxN+, G any
M1 NED allowed?	Yes	Yes	No	Yes
% M1 NED	5.8	14.4	n/a	4.0

RCC, renal cell carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; DFS, disease-free survival; RFS, recurrence-free survival; mo, months; HR, hazard ratio; CI, confidence interval; NR, not reached; n/a, not available; NED, no evidence of disease.

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Perioperative nivolumab versus observation in patients with renal cell carcinoma undergoing nephrectomy (PROSPER ECOG-ACRIN EA8143): an open-label, randomised, phase 3 study

www.thelancet.com/oncology **Published online June 25, 2024**

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- ***Clinical stage*** T2 or greater or T_{any} N+ renal cell carcinoma of clear cell or non-clear cell histology planned for partial or radical nephrectomy.
- Selected patients with oligometastatic disease, who were disease free at other disease sites within 12 weeks of surgery, were eligible for inclusion.

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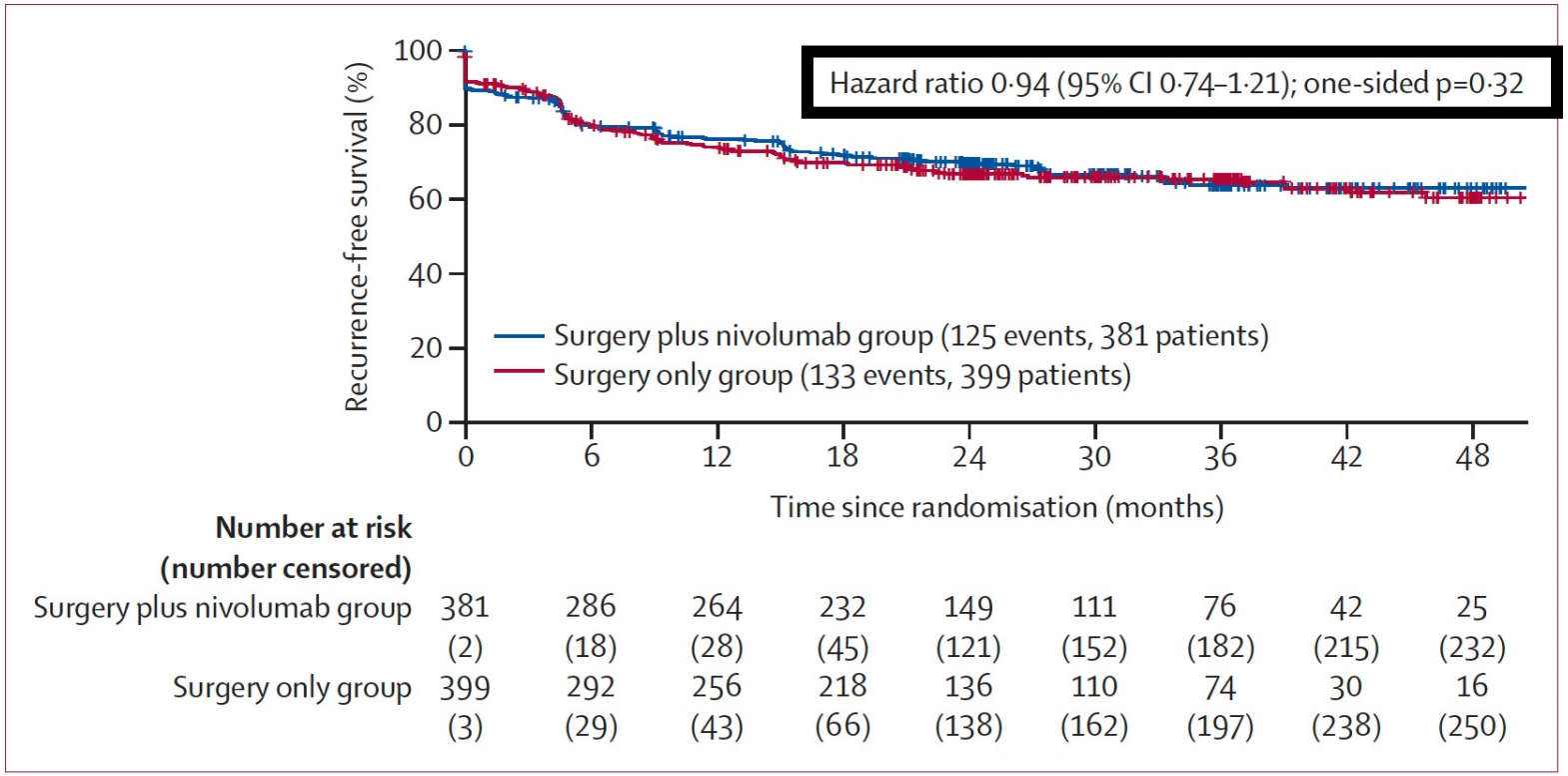

Number at risk (number censored)									
Surgery plus nivolumab group	381	286	264	232	149	111	76	42	25
	(2)	(18)	(28)	(45)	(121)	(152)	(182)	(215)	(232)
Surgery only group	399	292	256	218	136	110	74	30	16
	(3)	(29)	(43)	(66)	(138)	(162)	(197)	(238)	(250)

Figure 2: **Recurrence-free survival**

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ESTABLISHED IN 1812 AUGUST 19, 2021 VOL. 385 NO. 8

Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma

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- KN564 adjuvant pembro for histologically confirmed locoregional renal cell carcinoma with a clear-cell component
- Patients at high risk of recurrence (**pT2 with nuclear grade 4 or sarcomatoid differentiation; pT3 or higher, regional lymph-node metastasis, or stage M1 with NED**)

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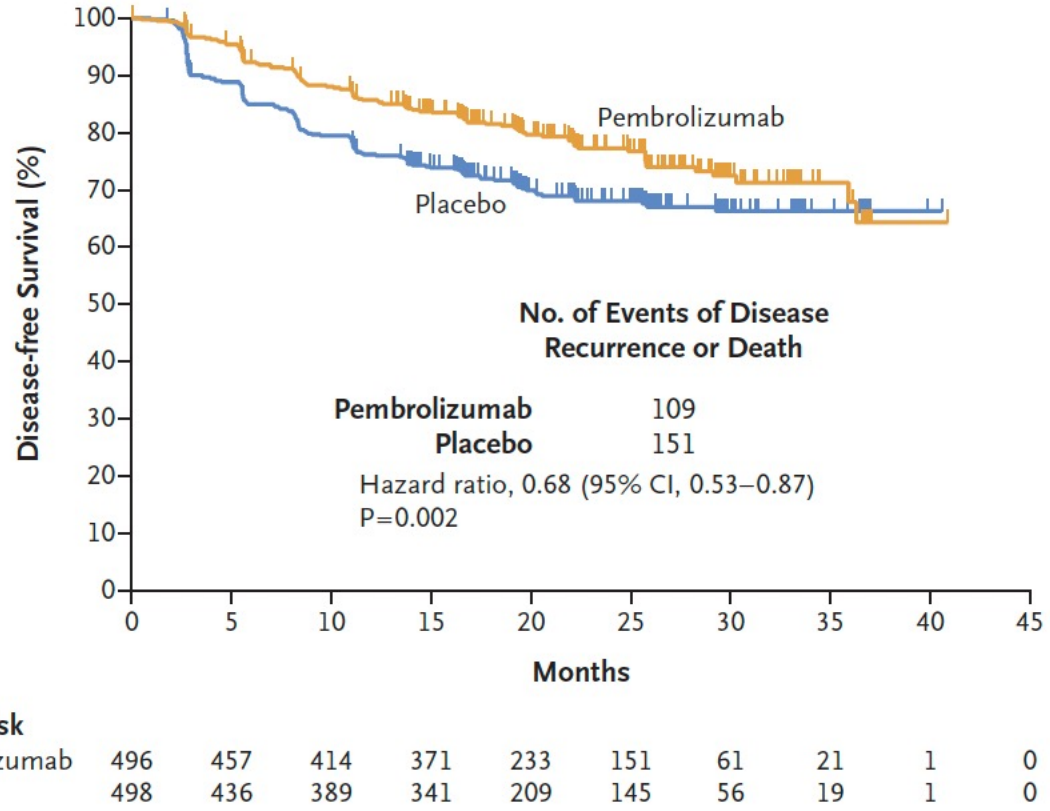
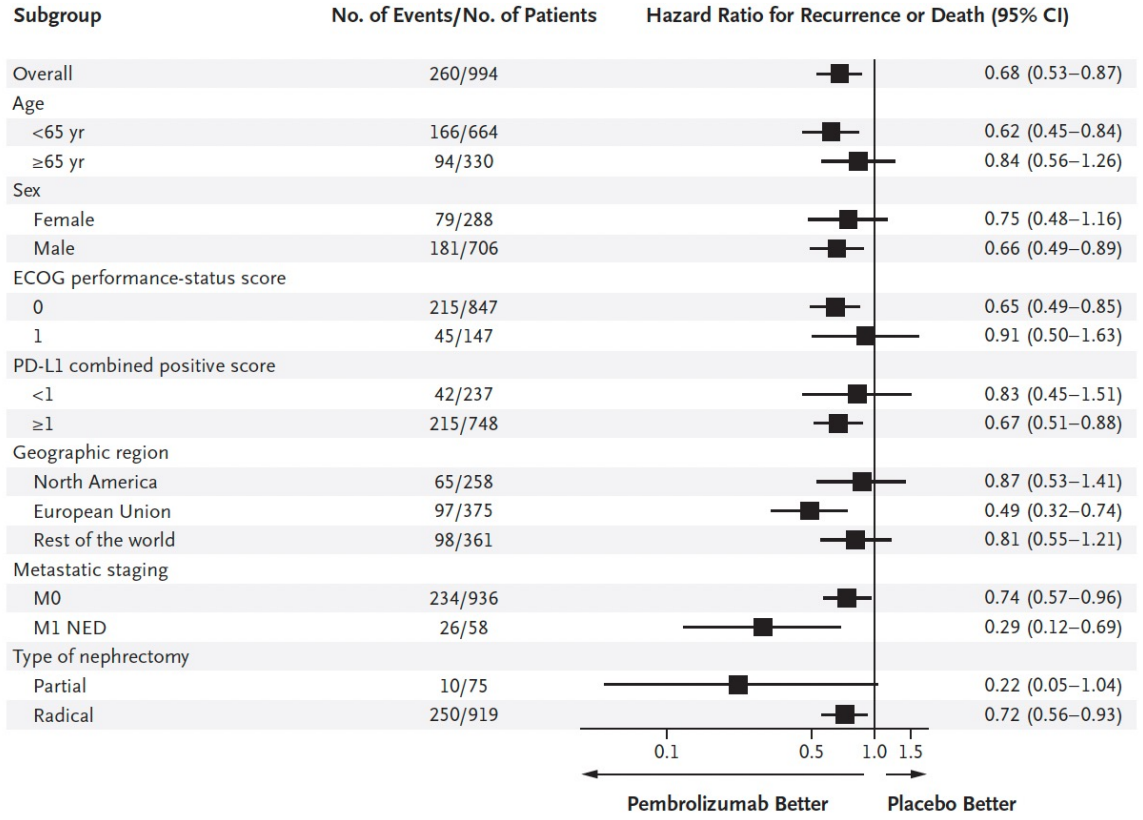
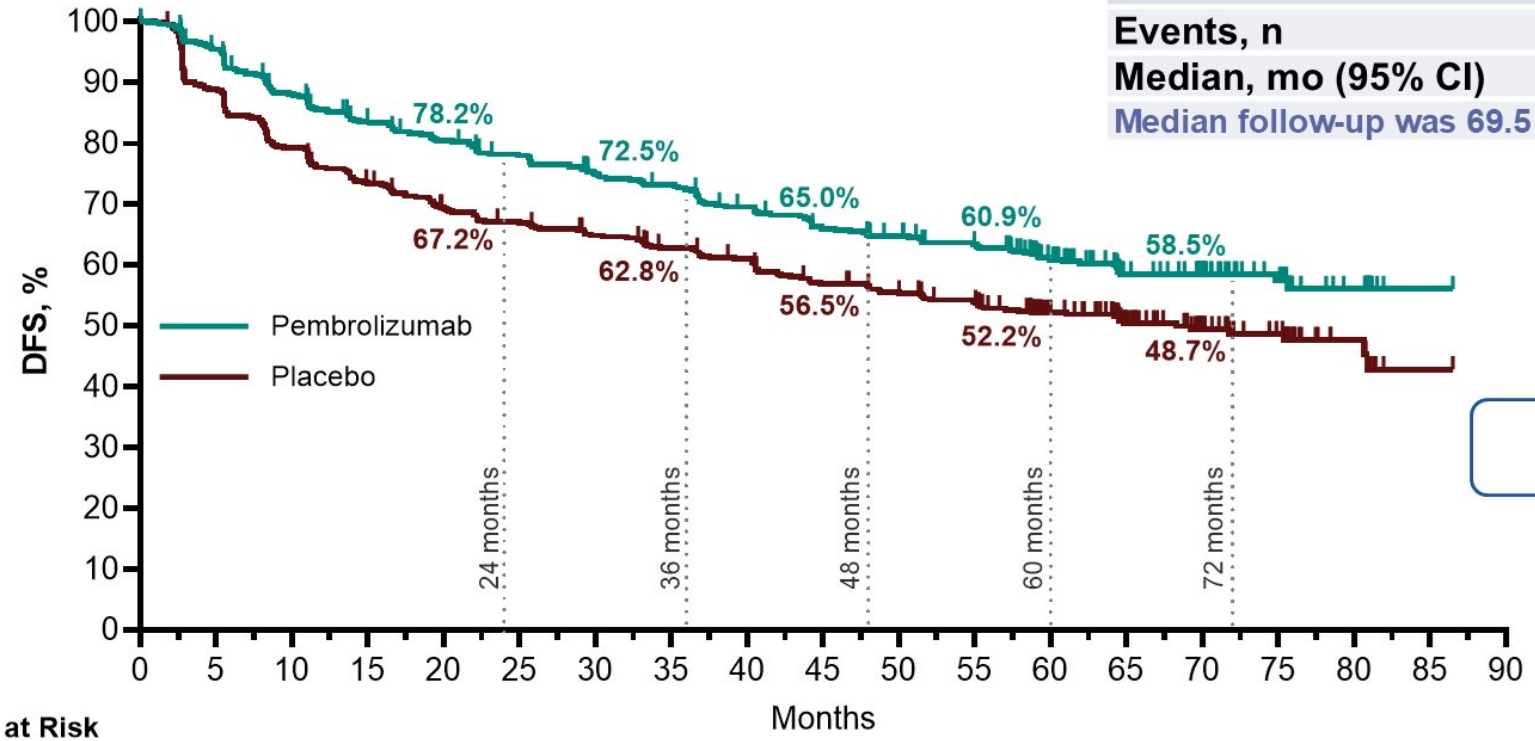




Phase III KEYNOTE-564: 5-Year Updated Disease-Free Survival

	Pembro (N = 496)	Placebo (N = 498)
Events, n	188	241
Median, mo (95% CI)	NR (NR–NR)	68.3 (51.7–NR)

Median follow-up was 69.5 months (range, 60.2–86.9)



HR 0.71 (95% CI 0.59–0.86)

No. at Risk																			
Pembrolizumab	496	459	417	388	371	356	338	328	309	291	282	269	207	128	88	63	26	1	0
Placebo	498	438	390	357	334	322	308	293	283	260	251	240	179	118	71	55	21	1	0

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

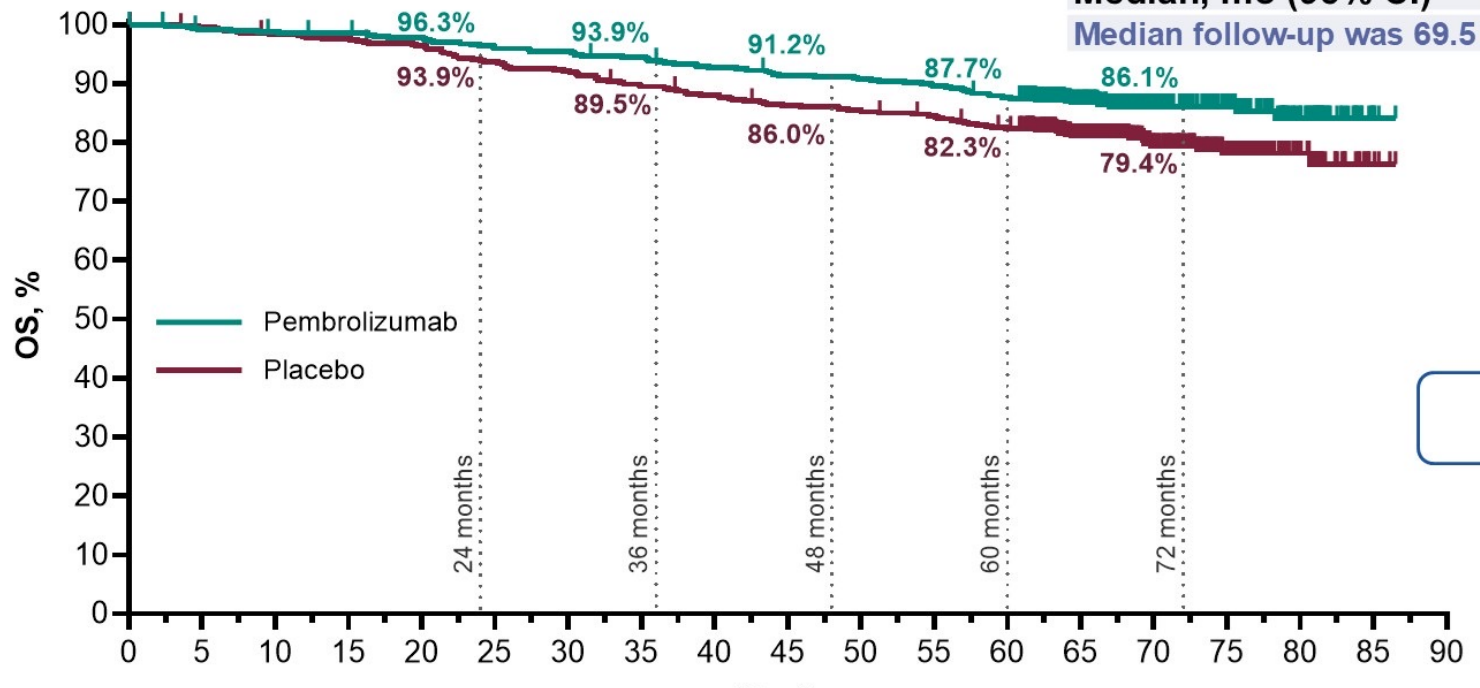
Data cutoff date: September 25, 2024.

Haas NB et al. ASCO 2025;Abstract 4515

Phase III KEYNOTE-564: 5-Year Updated Overall Survival

	Pembro (N = 496)	Placebo (N = 498)
Events, n	68	99
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)

Median follow-up was 69.5 months (range, 60.2–86.9)



HR 0.66 (95% CI 0.48–0.90)

No. at Risk																			
Pembrolizumab	496	489	486	484	479	470	468	462	452	445	442	436	426	310	198	121	50	3	0
Placebo	498	494	487	483	476	463	455	441	433	423	419	413	400	284	177	111	46	4	0

Key secondary OS endpoint was met at IA3 and was not formally statistically tested thereafter.

Data cutoff date: September 25, 2024.

Haas NB et al. ASCO 2025;Abstract 4515

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Future Directions

- Analyses of completed IO trials: KN564, PROSPER, Litespark 022
- Support ongoing adjuvant trial (STRIKE: adjuvant pembro +/- tivo)
- Participate in planning of periop trials (NEOSHIFT)

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Future Directions

- Consider frailty and opportunities for prehabilitation (CARE clinic)
- Competing mortality risk
- Nomogram for risk of irAE

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What do I do?

- Discuss the possibility of adjuvant therapy with all cT2-3 patients prior to surgery
- Discuss KN564 data with all eligible patients post-op
- Discuss STRIKE trial with all eligible patients

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What do I do?

- Discuss the possibility of adjuvant therapy with all cT2-3 patients prior to surgery
- Discuss KN564 data with all eligible patients post-op
- Discuss STRIKE trial with all eligible patients
- **Options: surveillance, Pembro monotherapy, Pembro +/- Tivo**

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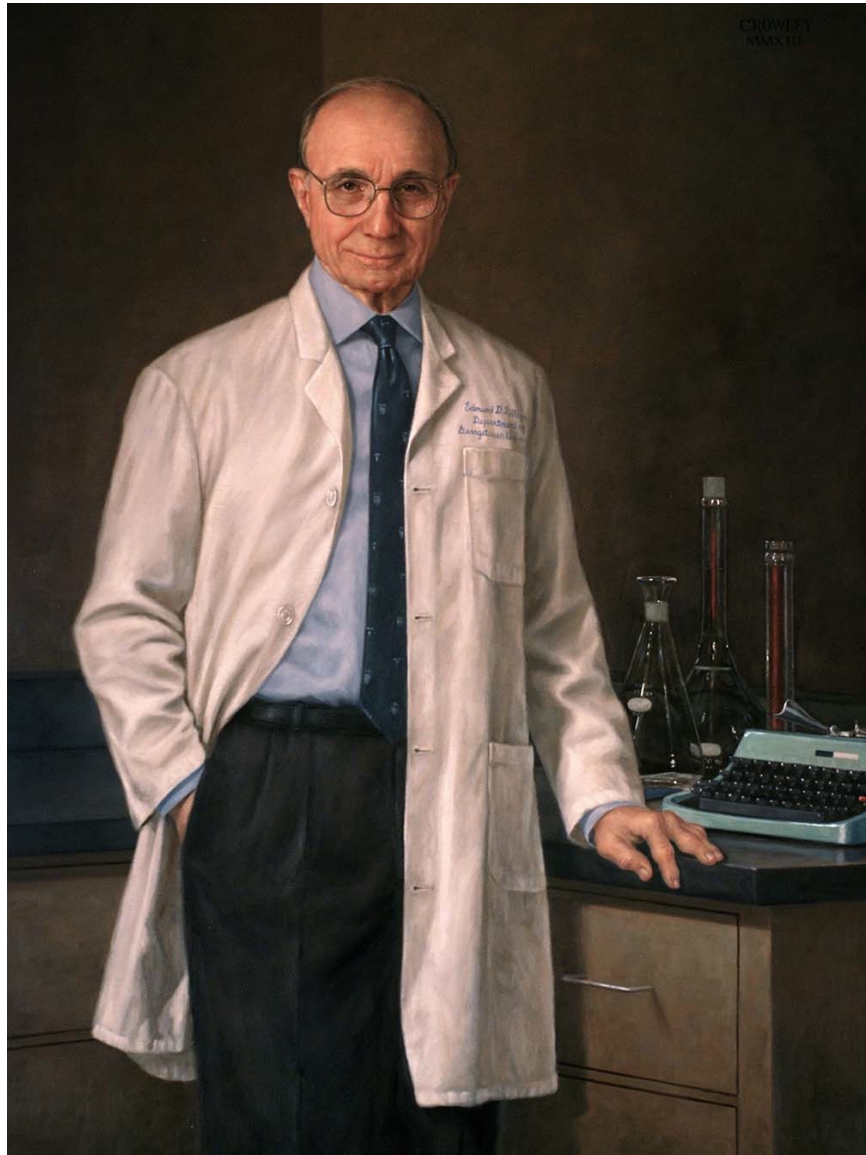
Why is Risk Stratification Needed?

Right and good healing action



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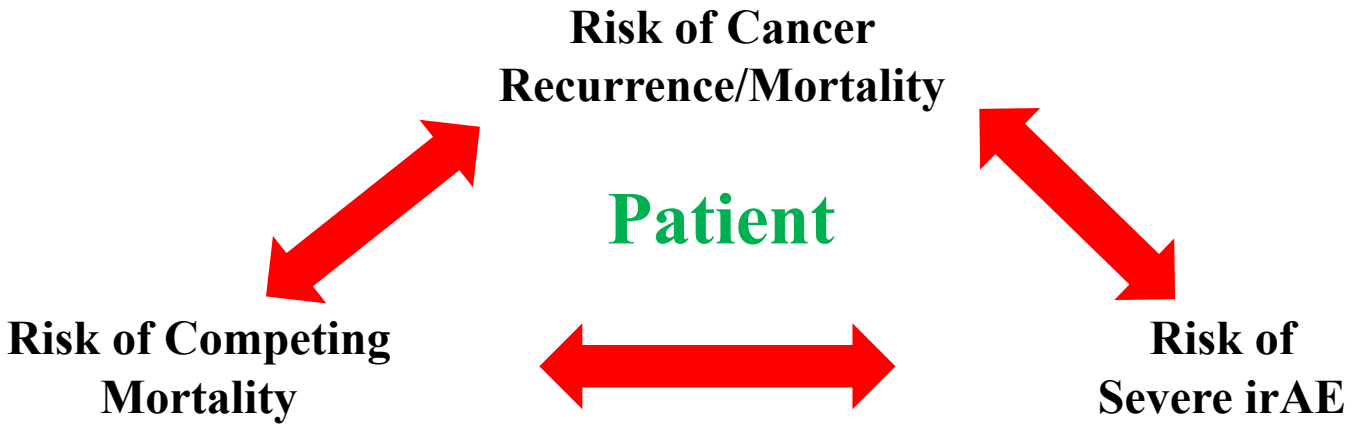

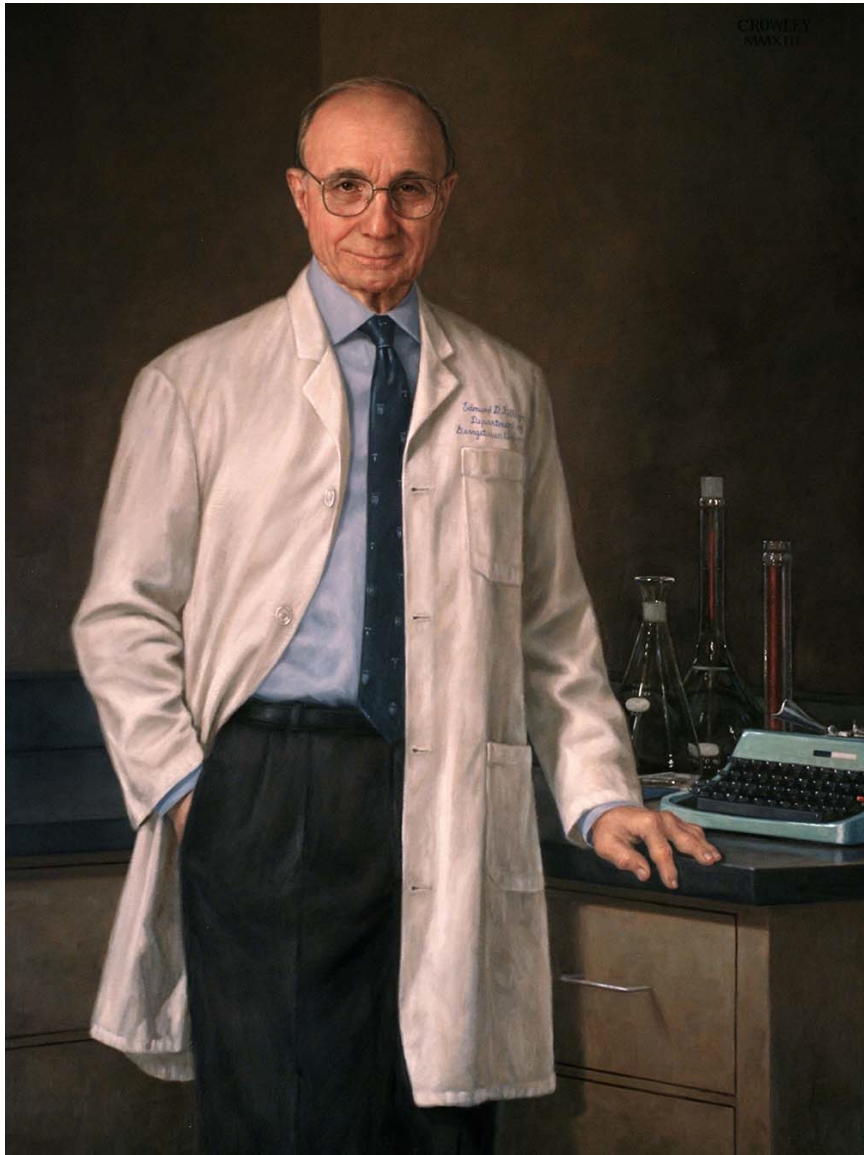

Second Opinion

Rana R McKay, MD, FASCO

Sandy Srinivas, MD

Neil Love, MD

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QUESTIONS FOR THE FACULTY

Which risk stratification models do you utilize when evaluating patients for consideration of adjuvant therapy?

In which situations, if any, do you assess ctDNA in the localized or metastatic RCC setting? Which assay or type of assay do you believe is most useful?

What is your usual approach to patients with resected M1 disease in terms of monitoring and the use of “pseudoadjuvant”systemic treatment?

Second Opinion

Andrew J Armstrong, MD, ScM

Rana R McKay, MD, FASCO

Neil Love, MD

RTP
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TO PRACTICE

QUESTIONS FOR THE FACULTY

Regulatory and reimbursement issues aside, how would you deploy the following in adjuvant and "pseudoadjuvant" situations?

- **Observation**
- **Pembrolizumab**
- **Pembrolizumab/belzutifan**

Regardless of your recommendation, would you discuss these 3 options with all eligible patients?

Agenda

Module 1: Current Indications for Adjuvant Immune Checkpoint Inhibitor Therapy in the Management of Renal Cell Carcinoma (RCC) — Dr Singer

Module 2: Potential Role of Hypoxia-Inducible Factor-2 Alpha (HIF-2α) Inhibitors as a Component of Adjuvant Treatment — Dr Hutson

Module 3: Tolerability of Current and Emerging Adjuvant Approaches for RCC — Dr Vaishampayan

Potential Role of Hypoxia-Inducible Factor-2 Alpha (HIF-2α) Inhibitors as a Component of Adjuvant Treatment

Thomas E Hutson, DO, PharmD, PhD FACP FASCO

Medical Oncology – Clinical Research/Drug Development

SCRI- GU Executive and Bridge Committees

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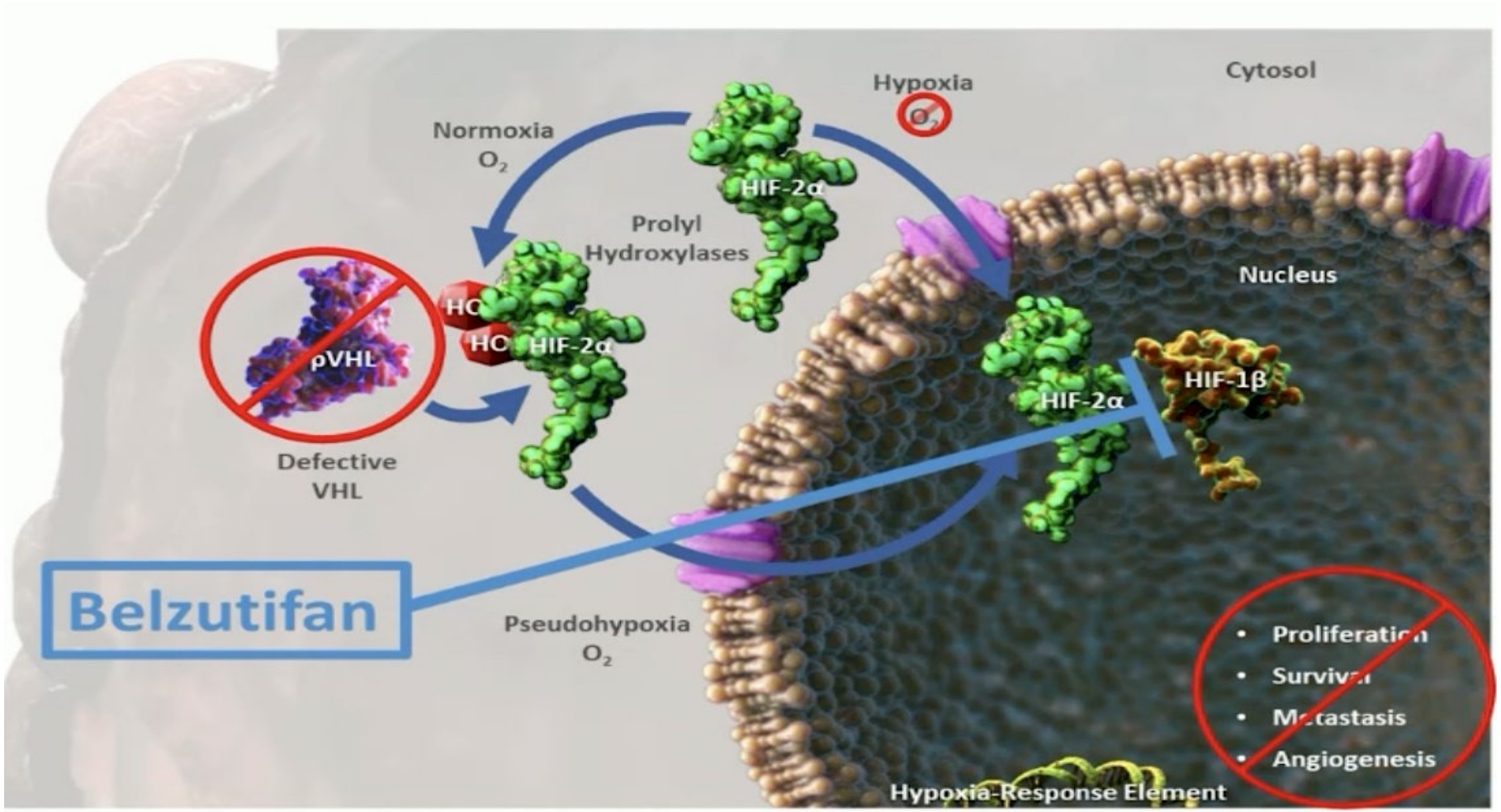
TOPICS

- Biological rationale for targeting HIF-2α in patients with RCC; mechanism of action of belzutifan
- Outcomes achieved with belzutifan in patients with advanced RCC and those with von Hippel-Lindau-associated disease
- Proposed synergy between belzutifan and PD-1 blockade by pembrolizumab
- Recently presented findings from the Phase III LITESPARK-022 trial assessing the addition of belzutifan to pembrolizumab in the adjuvant setting for patients with high-risk clear cell RCC

Biologic Rationale for targeting HIF-2a in patients with RCC: MOA



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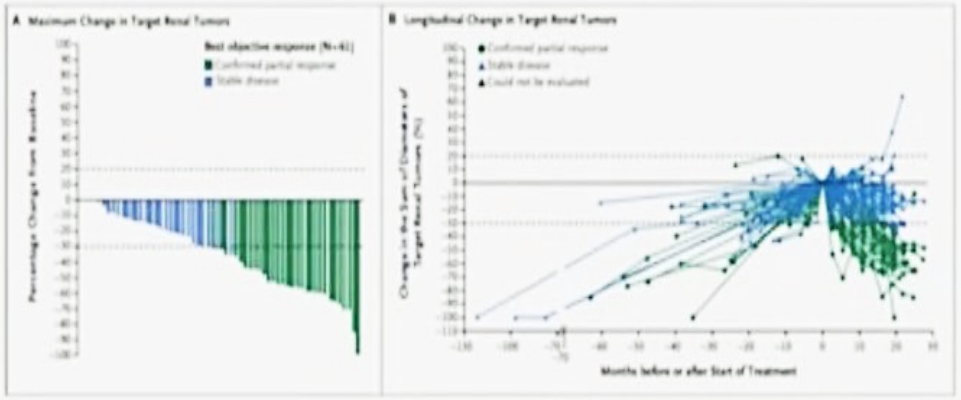
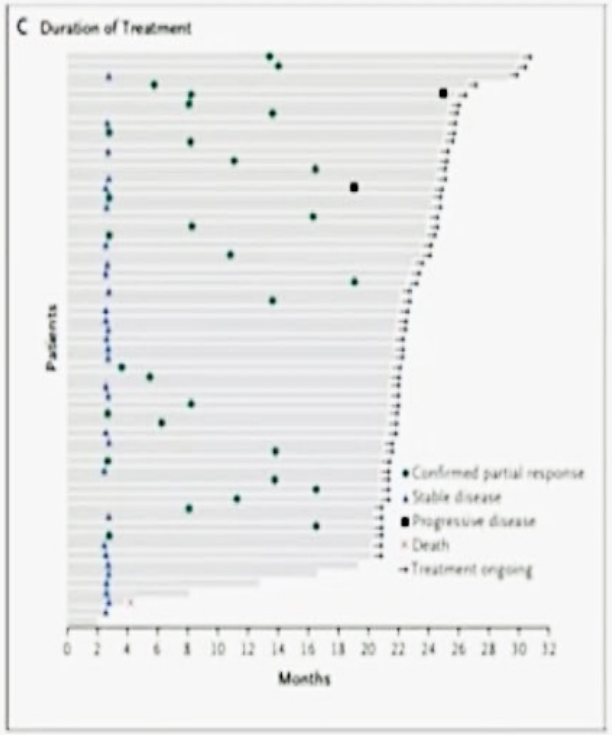
Belzutifan in VHL

Belzutifan for RCC Associated with VHL Disease



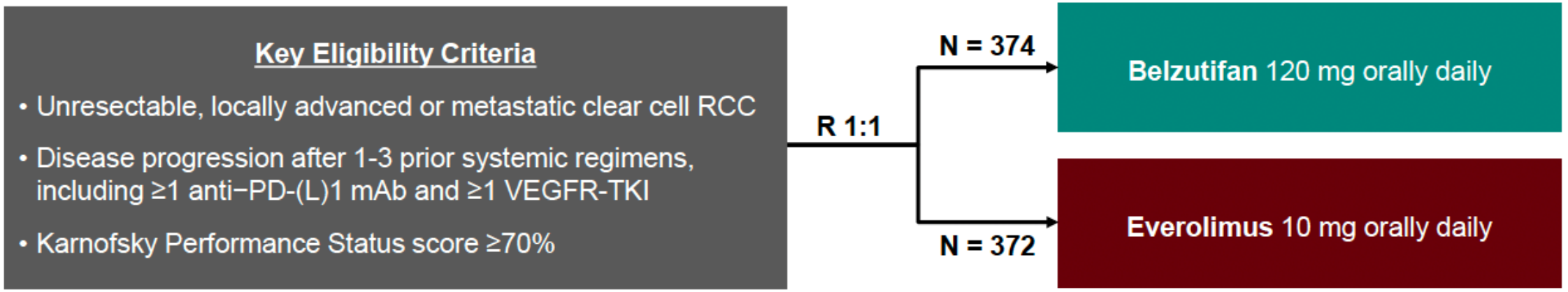


RCC ORR – 49%
RCC PD – 0%
RCC 24-month rPFS – 96%
Pancreatic lesions – 77%
CNS hemangioblastomas – 30%
Retinal hemangioblastomas – 100%

RCC=Renal cell carcinoma; VHL=Von Hippel Lindau; ORR=Objective response rate; PD=Progressive disease; rPFS=Radiographic progression-free survival; CNS=Central nervous system.

Jonasch et al, NEJM, 2021

Belzutifan in mRCC: LITESPARK-005



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

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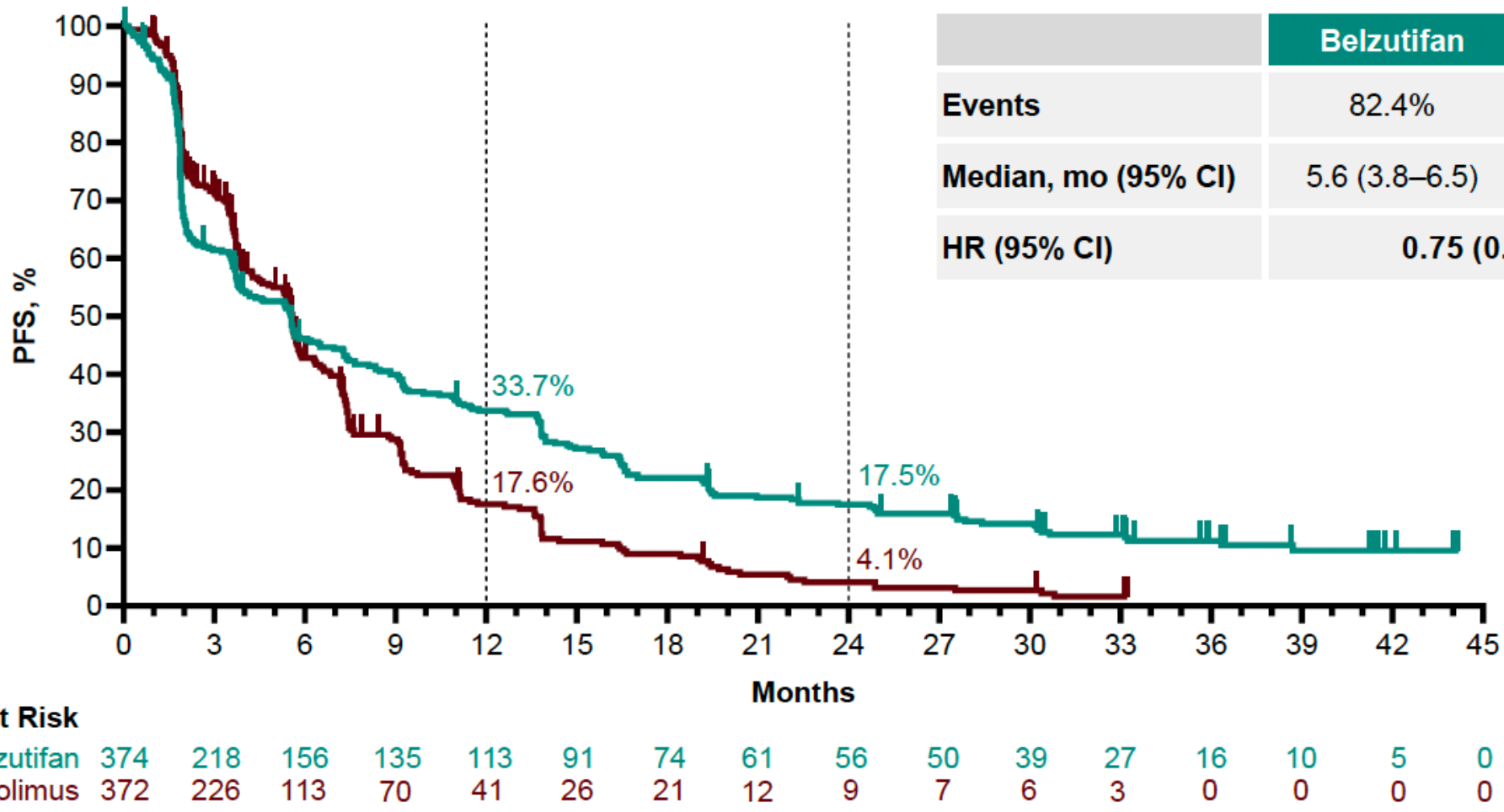
Rini BI et al. ESMO 2024;Abstract LBA74.

LITESPARK-005: PFS



	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)**	

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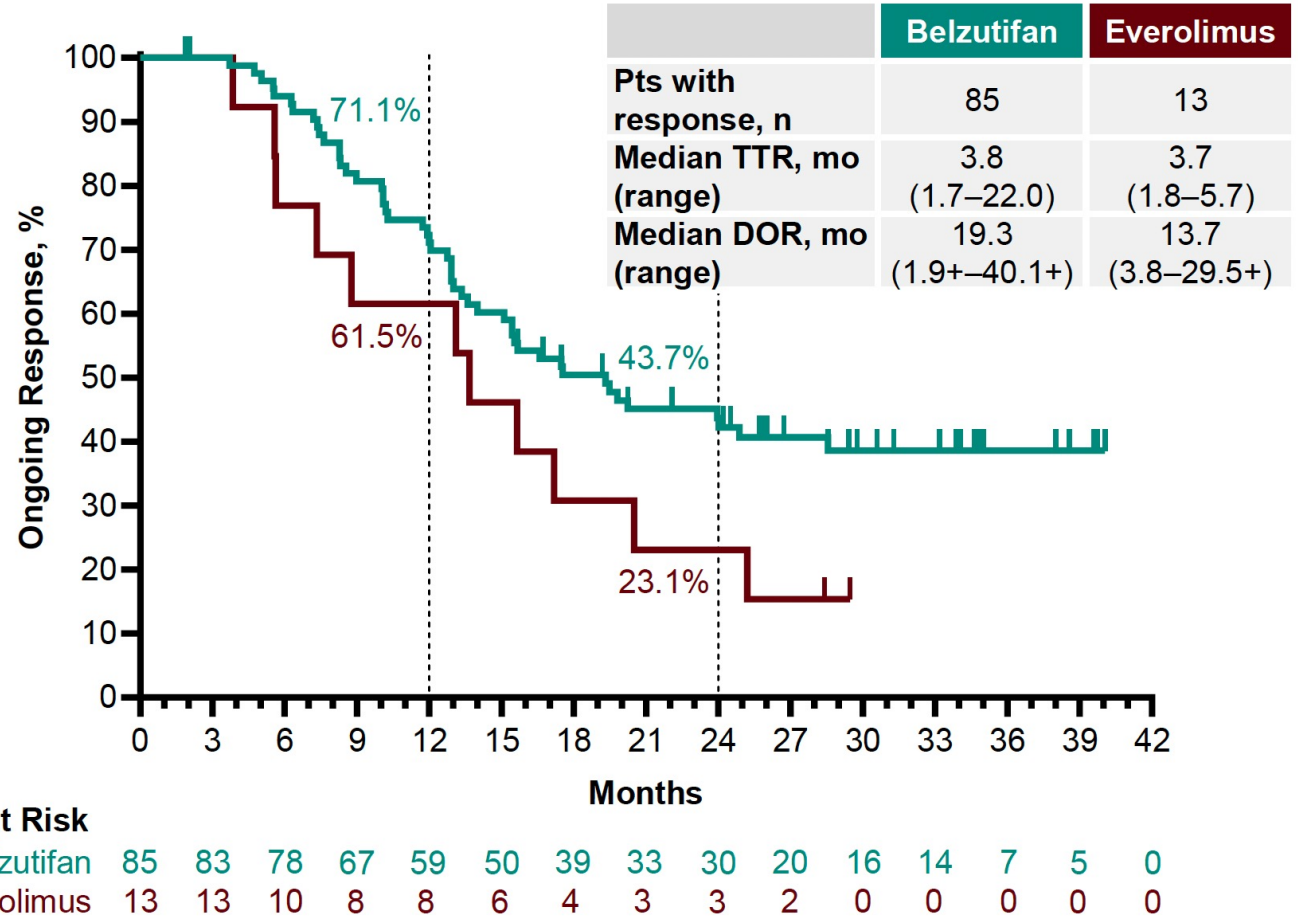
LITESPARK-005: ORR and DOR

	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%



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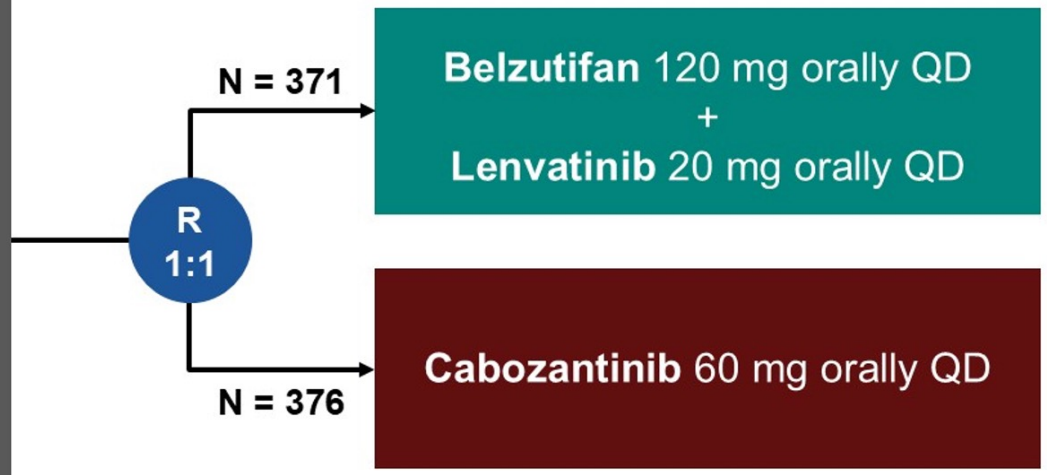
Belzutifan + Lenvatinib in mRCC: LITESPARK-011

Key Eligibility Criteria

- Unresectable, locally advanced or metastatic clear cell RCC
- Karnofsky Performance Status score ≥70%
- ≤2 prior systemic regimens
- Progression on/after anti−PD-(L)1 mAb as 1L or 2L therapy or progression ≤6 months of the last dose of adjuvant anti−PD-(L)1 mAb
- Prior VEGFR-TKI was permitted



Stratification Factors

- IMDC prognostic score:[a] 0 vs. 1-2 vs. 3-6
- Line of treatment for prior anti−PD-(L)1: 1L, adjuvant, neoadjuvant-adjuvant vs. 2L
- Geographic region: North America vs. western Europe vs. rest of world

Dual Primary Endpoints:

- PFS per RECIST 1.1 by BICR
- OS

Key Secondary Endpoint:

- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:

- DOR per RECIST 1.1 by BICR
- Safety

Exploratory Endpoints Include:

- Time to deterioration in patient-reported outcomes

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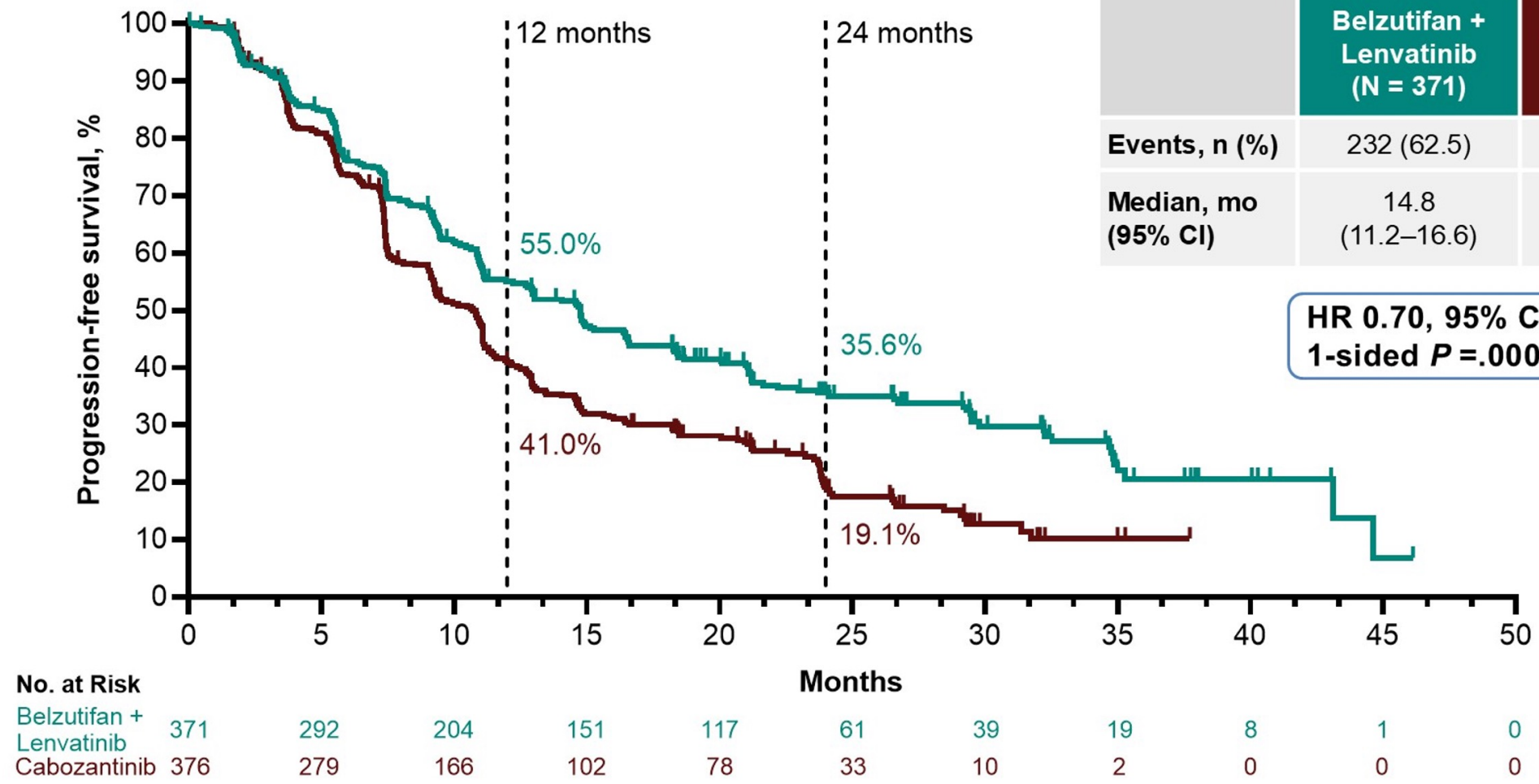
LITESPARK-011: PFS



	Belzutifan + Lenvatinib (N = 371)	Cabozantinib (N = 376)
Events, n (%)	232 (62.5)	273 (72.6)
Median, mo (95% CI)	14.8 (11.2–16.6)	10.7 (9.2–11.1)

HR 0.70, 95% CI 0.59–0.84, 1-sided *P* =.00007*

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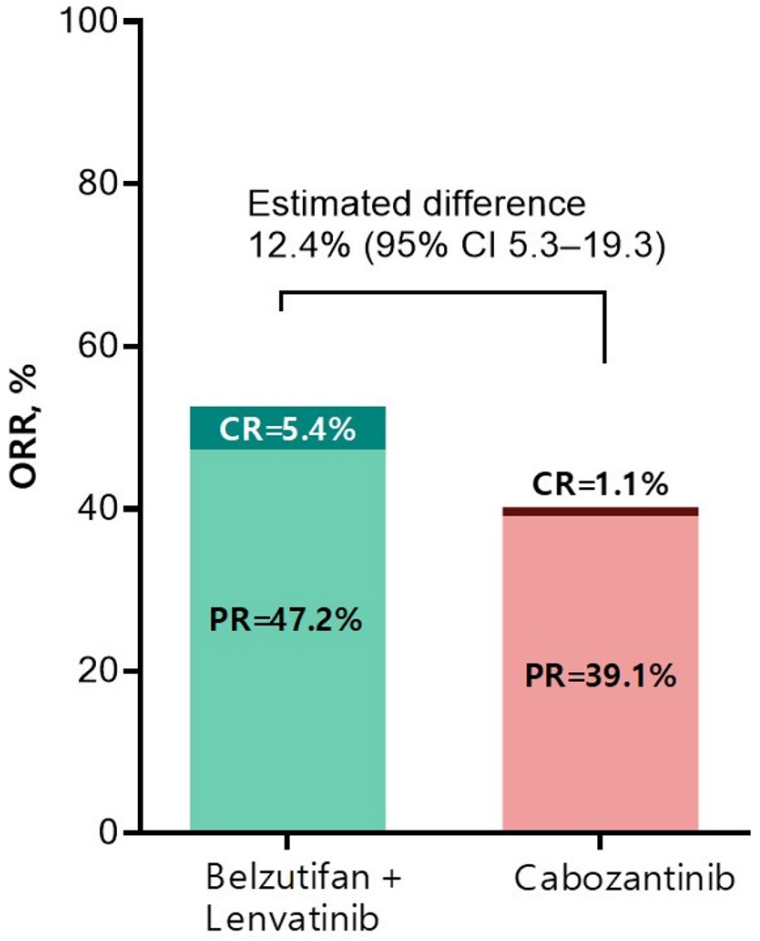
LITESPARK-011: ORR

	Belzutifan + Lenvatinib (N = 371)	Cabozantinib (N = 376)
ORR, % (95% CI)	52.6 (47.3–57.7)	40.2 (35.2–45.3)
Estimated difference, % (95% CI)	12.4 (5.3–19.3)[a]	
Best overall response		
CR	20 (5.4)	4 (1.1)
PR	175 (47.2)	147 (39.1)
SD	143 (38.5)	186 (49.5)
PD	21 (5.7)	22 (5.9)
Not evaluable[b]	4 (1.1)	7 (1.9)
No assessment[c]	8 (2.2)	10 (2.7)



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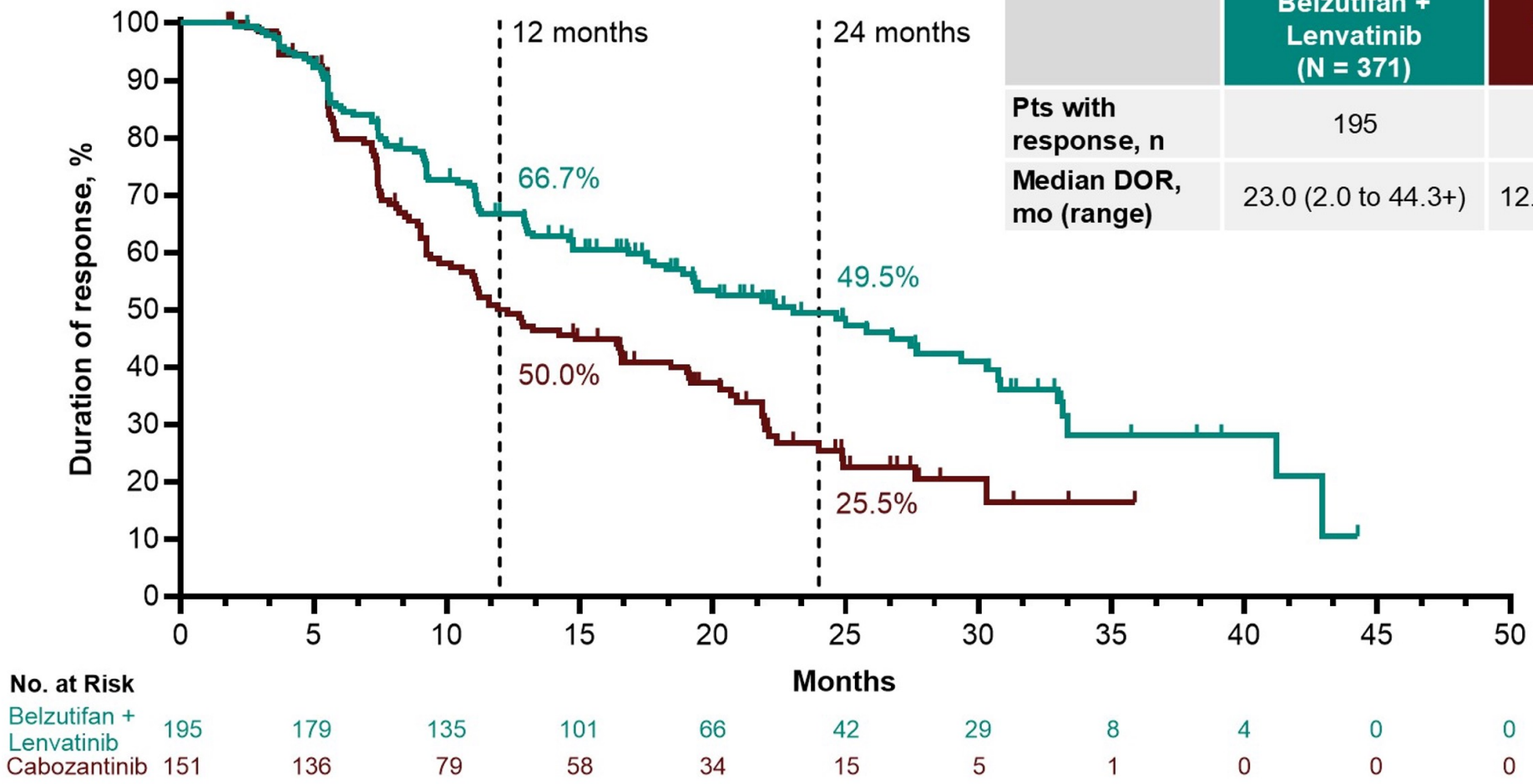
LITESPARK-011: DOR



	Belzutifan + Lenvatinib (N = 371)	Cabozantinib (N = 376)
Pts with response, n	195	151
Median DOR, mo (range)	23.0 (2.0 to 44.3+)	12.3 (1.8+ to 35.9+)

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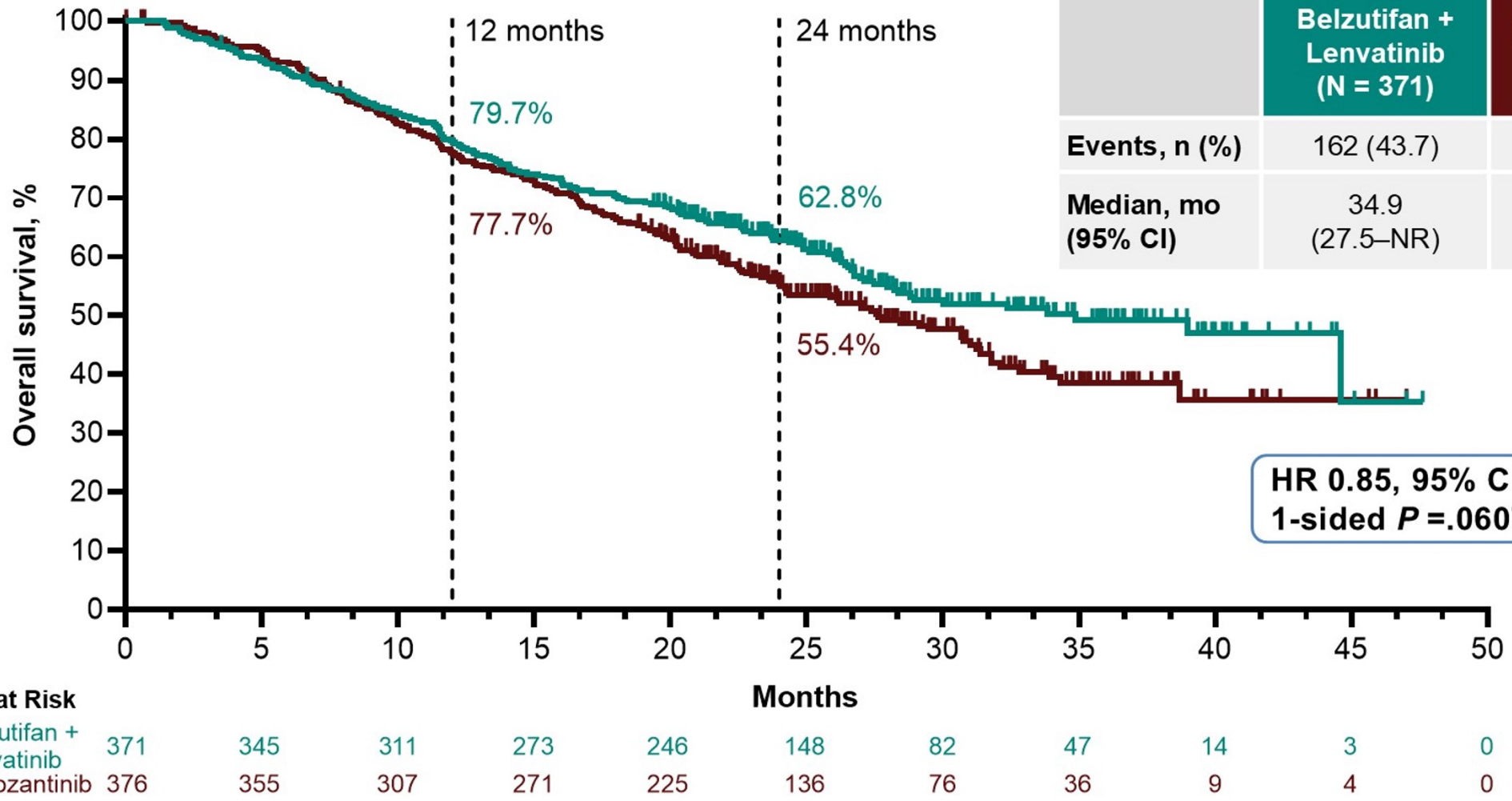
LITESPARK-011: OS



	Belzutifan + Lenvatinib (N = 371)	Cabozantinib (N = 376)
Events, n (%)	162 (43.7)	192 (51.1)
Median, mo (95% CI)	34.9 (27.5–NR)	27.6 (24.0–31.4)

HR 0.85, 95% CI 0.68–1.05, 1-sided *P* =.06075

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Proposed Synergy between Belzutifan and Pembro

Belzutifan

HIF-2α Inhibitor

- Blocks hypoxia-inducible factor 2-alpha
- Reduces VEGF production
- Normalizes tumor vasculature
- Decreases immunosuppressive factors
- Reduces myeloid-derived suppressor cells (MDSCs)

Pembrolizumab

PD-1 Checkpoint Inhibitor

- Blocks PD-1/PD-L1 interaction
- Restores T-cell activation
- Enhances anti-tumor immunity
- Promotes cytotoxic T-cell function
- Overcomes immune evasion

Synergistic Mechanisms

Enhanced T-cell infiltration: Belzutifan normalizes vasculature → improved T-cell trafficking

Reduced immunosuppression: HIF-2α inhibition decreases MDSCs and Tregs → pembrolizumab works better

Improved tumor microenvironment: Less hypoxia → more favorable for immune response

Complementary pathways: Targeting both metabolic and immune checkpoints

Phase 3 LITESPARK-022: Adjuvant Pembrolizumab + Belzutifan

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

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Phase 3 LITESPARK-022: Patient Characteristics

Characteristic, n (%)	Pembrolizumab + belzutifan (N = 921)	Pembrolizumab + placebo (N = 920)
Age, median (range), yrs	59.0 (20–91)	60.0 (24–86)
Sex		
Male	673 (73.1)	642 (69.8)
Female	248 (26.9)	278 (30.2)
US Region		
US	140 (15.2)	115 (12.5)
Non-US	781 (84.8)	805 (87.5)
Race		
White	576 (62.5)	581 (63.2)
All others	303 (32.9)	315 (34.2)
Missing	42 (4.6)	24 (2.6)
ECOG PS		
0	788 (85.6)	777 (84.5)
1	133 (14.4)	143 (15.5)

Characteristic, n (%)	Pembrolizumab + belzutifan (N = 921)	Pembrolizumab + placebo (N = 920)
Risk Category[a]		
Intermediate-to-High	779 (84.6)	782 (85.0)
High	58 (6.3)	53 (5.8)
M1 NED	84 (9.1)	84 (9.1)
Sarcomatoid features		
Present	104 (11.3)	84 (9.1)
Absent	730 (79.3)	724 (78.7)
Unknown	87 (9.4)	112 (12.2)
Tumor grade		
1-2	322 (35.0)	328 (35.7)
3-4	599 (65.0)	592 (64.3)
PD-L1 status[b]		
CPS <1	222 (24.1)	217 (23.6)
CPS ≥1	547 (59.4)	502 (54.6)
Not available[c]	152 (16.5)	201 (21.8)

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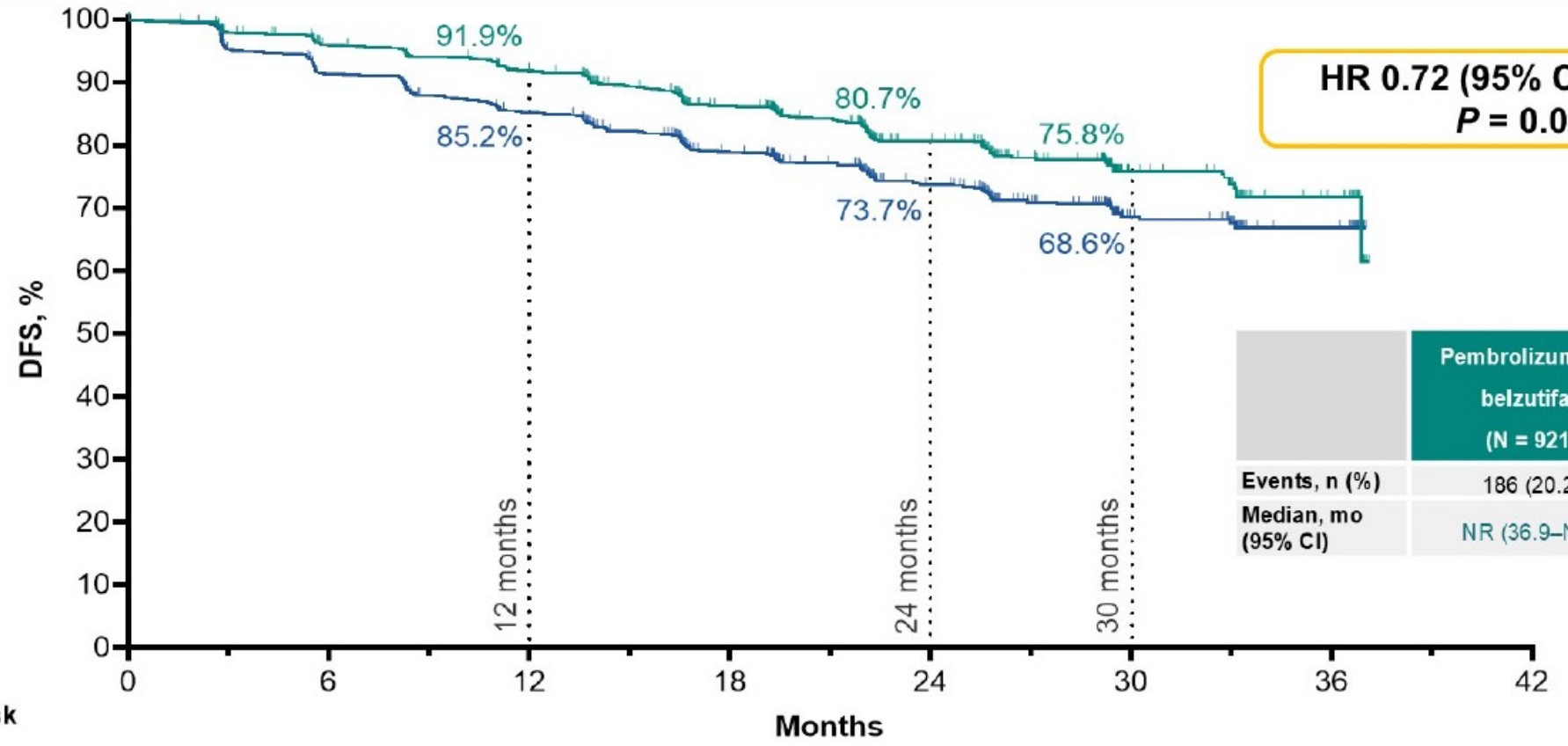
Phase 3 LITESPARK-022: DFS



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

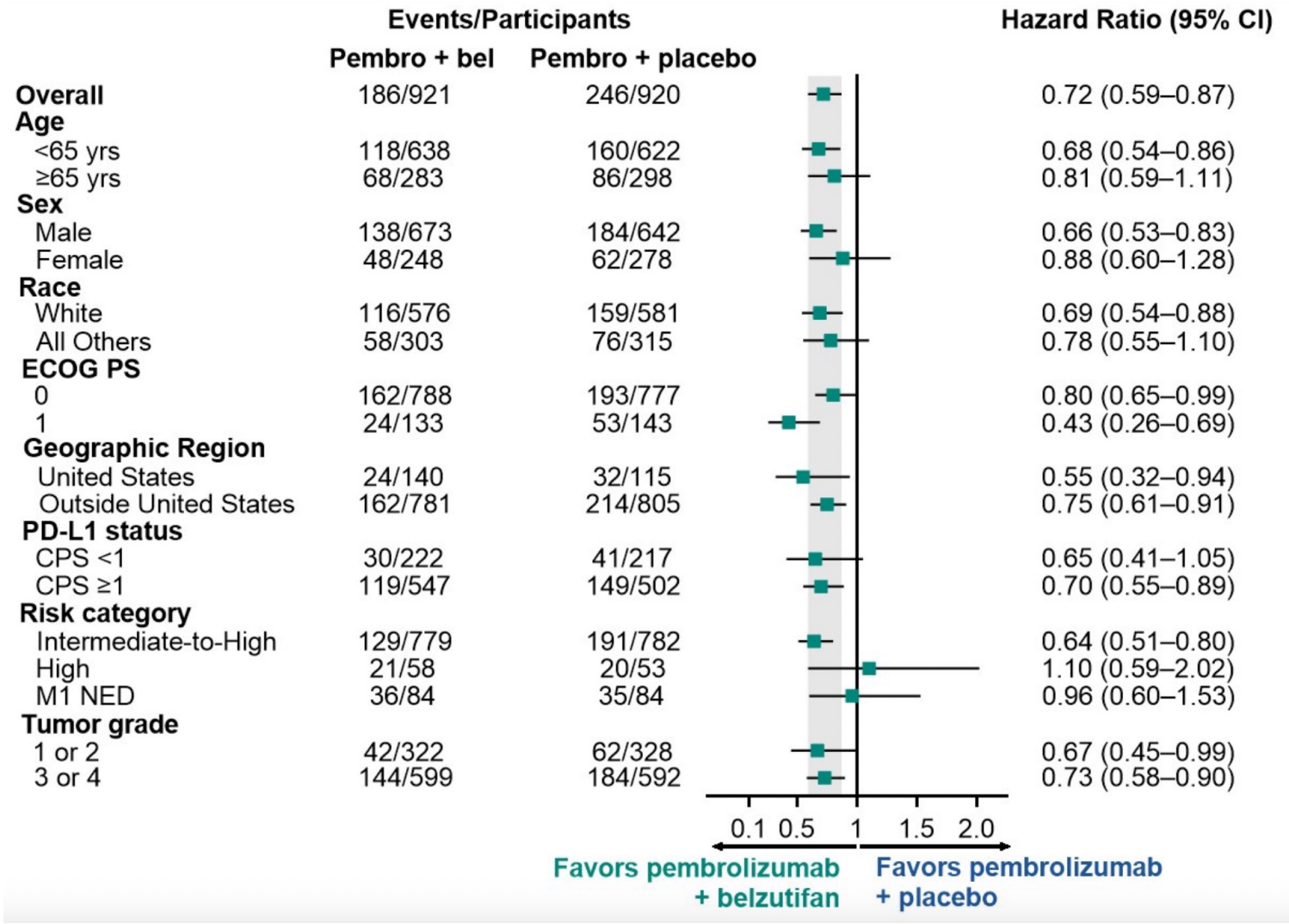
Pembrolizumab + belzutifan	921	850	805	669	451	153	35	0
Pembrolizumab + placebo	920	823	759	619	417	140	38	0

*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 TK et al. ASCO GU 2026;Abstract LBA418.

Phase 3 LITESPARK-022: DFS Subgroup Analysis



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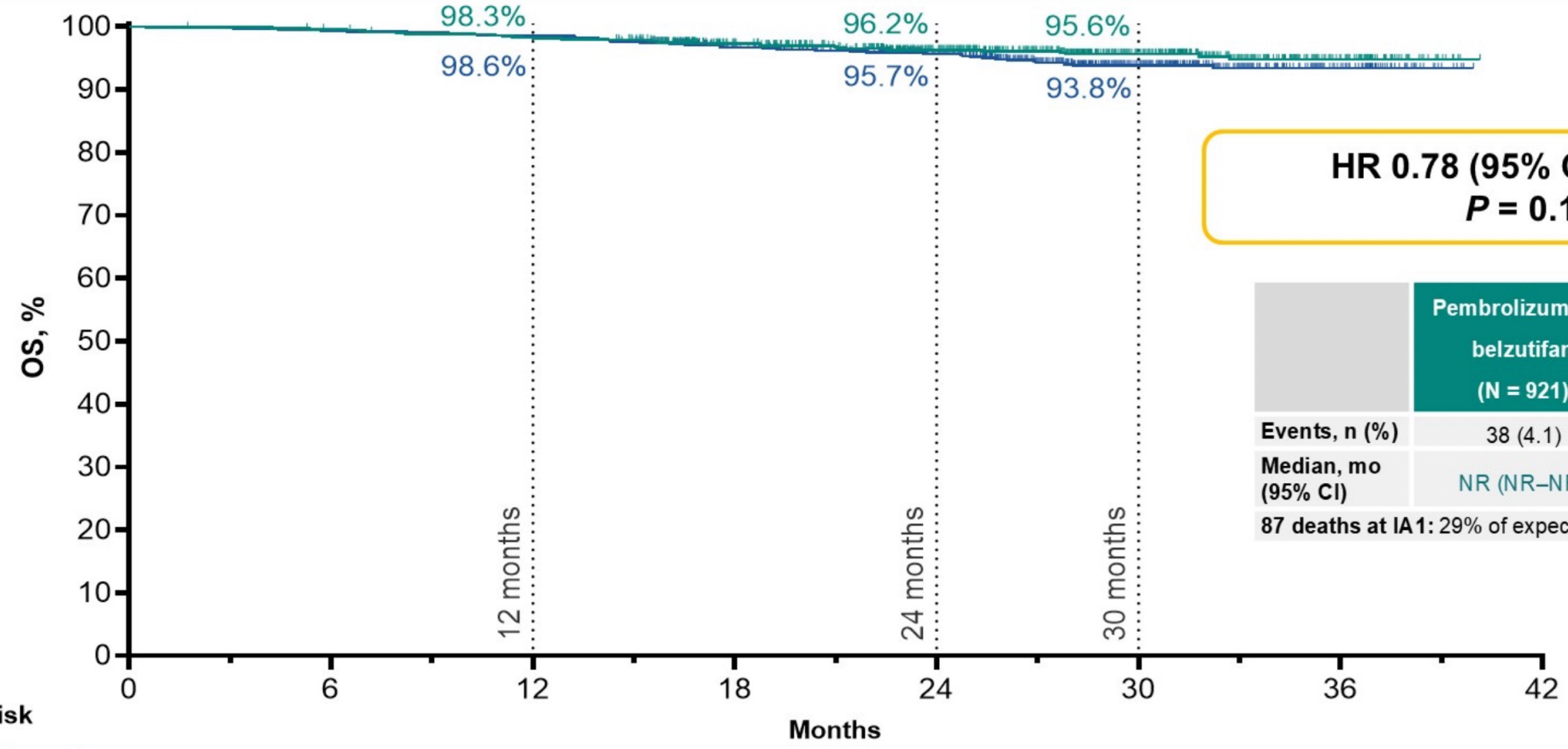
Phase 3 LITESPARK-022: Interim OS



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).
Data cutoff: August 23, 2025.

Choueiri TK et al. ASCO GU 2026;Abstract LBA418.

Phase 3 LITESPARK-022: Summary

- Pembrolizumab + belzutifan showed a statistically significant and clinically meaningful DFS improvement vs pembrolizumab monotherapy in participants with ccRCC at increased risk of recurrence post nephrectomy
  - DFS benefit was generally consistent across prespecified subgroups
- Additional follow-up is planned for the key secondary endpoint of OS
- The safety profile of pembrolizumab + belzutifan was manageable with a low rate of AEs leading to the discontinuation of both study drugs
  - Overall safety was consistent with the expected profiles of each individual drug
- LITESPARK-022 is the first adjuvant phase 3 trial in RCC to show a significant benefit for a combination treatment vs an active immunotherapy comparator
- These results support the addition of belzutifan to standard-of-care adjuvant pembrolizumab for patients with ccRCC at increased risk of recurrence

Choueiri TK et al. ASCO GU 2026;Abstract LBA418.

Second Opinion

Robert J Motzer, MD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Based on available data, would you like to be able to administer adjuvant pembrolizumab/belzutifan to any of your patients at this time, or would you prefer to wait until overall survival has been documented? If yes, which specific patients?

Would you consider reserving belzutifan for the second-line or later metastatic setting based on the data from the LITESPARK-005 or LITESPARK-011 studies? In general, what are your thoughts on rechallenging with belzutifan if a patient previously received adjuvant pembrolizumab/belzutifan?

Second Opinion

Andrew J Armstrong, MD, ScM

Sandy Srinivas, MD

Rana R McKay, MD, FASCO

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What comorbidities, if any, do you consider relative or absolute contraindications to the use of belzutifan in the adjuvant setting?

How do you approach the use of belzutifan for patients living at high altitudes? How do you define high altitude, and do you hold the drug for patients who travel to these areas?

How will you approach the prevention and management of anemia in patients receiving belzutifan in the adjuvant setting?

What is the minimum baseline Hb for which you would use the drug?

Is there any particular advice you give to patients regarding diet and exercise while receiving adjuvant pembrolizumab/belzutifan?

Agenda

Module 1: Current Indications for Adjuvant Immune Checkpoint Inhibitor Therapy in the Management of Renal Cell Carcinoma (RCC) — Dr Singer

Module 2: Potential Role of Hypoxia-Inducible Factor-2 Alpha (HIF-2α) Inhibitors as a Component of Adjuvant Treatment — Dr Hutson

Module 3: Tolerability of Current and Emerging Adjuvant Approaches for RCC — Dr Vaishampayan

Tolerability of Current and Emerging Adjuvant Approaches for RCC

Ulka Vaishampayan, M.D.

Director of Phase I Therapeutics

Rogel Cancer Center

Professor of Medicine/GU Oncology

University of Michigan School of Medicine

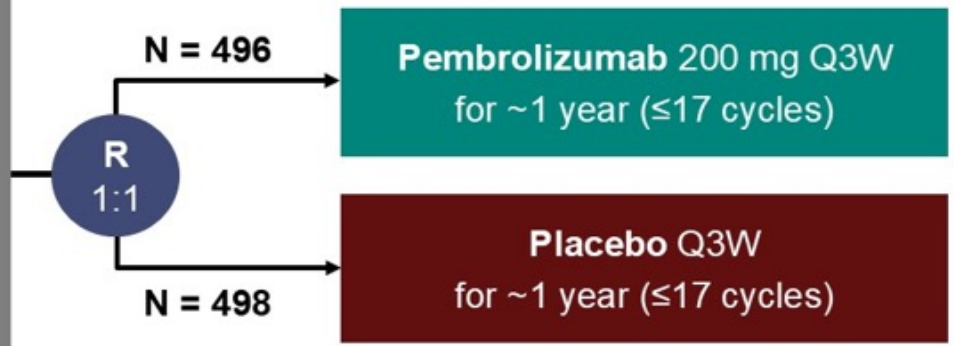
Ann Arbor MI

KEYNOTE-564: Study Design

Key Eligibility Criteria

- Histologically confirmed clear cell RCC with no prior systemic therapy
- Surgery ≤12 weeks prior to randomization
- Postnephrectomy intermediate-high risk of recurrence (M0):
  - pT2, grade 4 or sarcomatoid, N0
  - pT3, any grade, N0
- Postnephrectomy high risk of recurrence (M0):
  - pT4, any grade, N0
  - Any pT, any grade, N+
- Postnephrectomy + complete resection of metastasis (M1 NED)
- ECOG PS 0 or 1

Median follow-up to data cutoff (Sept 25, 2024):
69.5 months (range, 60.2–86.9)



Stratification Factors

- M stage (M0 vs. M1 NED)
- M0 group further stratified:
  - ECOG PS 0 vs. 1
  - US vs. non-US

Primary Endpoint

- Disease-free survival (DFS) by investigator

Key Secondary Endpoint

- Overall survival (OS)

Other Secondary Endpoints

- Safety

Haas N et al. ASCO 2025

KEYNOTE-564: Updated Safety Findings at Five-Year Follow Up

	IA3 (57.2 mo follow-up)		IA4 (69.5 mo follow-up)	
	Pembro (N = 488)	Placebo (N = 496)	Pembro (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	156 (32.0%)	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%)
Any-cause 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%)	263 (53.0%)	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
Treatment-related serious AEs[a]	59 (12.1%)	1 (0.2%)	58 (11.9%)	1 (0.2%)
Immune-mediated AEs and infusion reactions[b,c]	178 (36.5%)	36 (7.3%)	179 (36.7%)	36 (7.3%)
Grade 3 to 4	46 (9.4%)	3 (0.6%)	47 (9.6%)	3 (0.6%)
Led to death	0	0	0	0

Haas N et al. ASCO 2025

KEYNOTE-564: Updated Safety Findings at Five-Year Follow Up

	Pembro (N = 488)		Placebo (N = 496)	
	n (%)	Median duration,[a] days (Q1-Q3)	n (%)	Median duration,[a] days (Q1-Q3)
Any grade 3-5 AE	75 (15.4)	39 (18–107)	24 (4.8)	36 (7–82)
Hypertension	14 (2.9)	43 (22–NE)	13 (2.6)	38 (4–NE)
Alanine aminotransferase increased	11 (2.3)	32 (22–47)	1 (0.2)	64 (64–64)
Diarrhea	9 (1.8)	22 (2–50)	1 (0.2)	4 (4–4)
Aspartate aminotransferase increased	8 (1.6)	33 (22–59)	1 (0.2)	7 (7–7)
Pneumonia	7 (1.4)	5 (3–16)	1 (0.2)	19 (19–19)
Hyperglycemia	6 (1.2)	64 (29.5–139.5)	3 (0.6)	52 (22–63)
Adrenal insufficiency	6 (1.2)	78.5 (39–101)	1 (0.2)	4 (4–4)
Acute kidney injury	5 (1.0)	17 (9–365)	0	-
Colitis	5 (1.0)	140 (48–169)	0	-
Diabetic ketoacidosis	5 (1.0)	14 (7–30)	0	-
Fatigue	5 (1.0)	546 (122–NE)	0	-
Lipase increased	5 (1.0)	44.5 (22–85)	0	-
Type 1 diabetes mellitus	5 (1.0)	45 (21–241)	0	-
Hyponatremia	2 (0.4)	6 (4–8)	6 (1.2)	36 (20–NE)

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NCCN Guidelines: Management of ICI-Related Toxicities

PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE CHECKPOINT INHIBITORS

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Clinical • Physical examination • Patient and relevant family history of any autoimmune/ organ-specific disease, endocrinopathy, or infectious disease (ID) • Neurologic examination • Bowel habits (typical frequency/consistency) • ID screening (human immunodeficiency virus [HIV]; hepatitis A, B, C) as indicated	Clinical examination at each visit with adverse event (AE) symptom assessment	Follow-up testing based on findings, symptoms
Imaging • Cross-sectional imaging • Brain MRI if indicated	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
General blood work • Complete blood count (CBC) (with differential if indicated) • Comprehensive metabolic panel (CMP)	Repeat prior to each treatment or every 4 weeks during immunotherapy, then in 6–12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic (ICI_DERM-1) • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms	Consider dermatology referral. Monitor affected skin and lesion type; photographic documentation. Skin biopsy if indicated.
Pancreatic (ICI_ENDO-1) • Baseline testing is not required	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal CT with contrast or MRCP for suspected pancreatitis
Thyroid (ICI_ENDO-2) • Thyroid-stimulating hormone (TSH), free thyroxine (FT4)	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	ICI_ENDO-2

NCCN Guidelines. Version 1.2026. Management of ICI-Related Toxicities

NCCN Guidelines: Management of ICI-Related Toxicities

PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE CHECKPOINT INHIBITORS

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Pituitary/Adrenal (ICI_ENDO-3) • Consider serum cortisol (morning preferred) and thyroid function as above	Consider repeating every 4–6 weeks during immunotherapy (immuno-oncology [IO]-only regimens[c]), then follow-up every 12 weeks as indicated	Morning serum cortisol, adrenocorticotropic hormone (ACTH), TSH, FT4, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, estradiol (premenopausal individuals), and cosyntropin stimulation test only as indicated
Fertility • Advise on family planning and refer to fertility preservation specialists if desired		
Pulmonary (ICI_PULM-1) • Oxygen saturation (resting and with ambulation) • Consider pulmonary function tests (PFTs) with diffusion capacity for patients who are high risk (eg, interstitial lung disease [ILD] on imaging, chronic obstructive pulmonary disease [COPD], previous suspected treatment-related lung toxicity) • In the absence of prior imaging, consider a chest x-ray	Repeat oxygen saturation tests based on symptoms	Chest CT with contrast to evaluate for pneumonitis, biopsy, or bronchoscopy with bronchoalveolar lavage (BAL) if needed to exclude other causes
Cardiovascular (ICI_CARDIO-1) • Consider baseline electrocardiogram (ECG) • Consider high-sensitivity troponin and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) • Individualized assessment in consultation with cardiology as indicated	Consider periodic testing for those with abnormal baseline or symptoms[d]	Individualized follow-up in consultation with cardiology as indicated
Musculoskeletal (ICI_MS-1) • Joint examination/functional assessment as needed for patients with pre-existing disease	No routine monitoring needed if asymptomatic	Consider rheumatology referral. Depending on clinical situation, consider C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or creatine kinase (CK)

NCCN Guidelines. Version 1.2026. Management of ICI-Related Toxicities

NCCN Guidelines: Management of ICI-Related Toxicities

General Principles

- Close consultation with disease-specific subspecialties is encouraged.
  - Referral to a tertiary care center may be required for management of complex cases or multi-system irAEs.
- Selected irAEs including hypothyroidism and other endocrine irAEs may be treated with hormonal supplementation, without the need for steroid therapy. See Endocrine Toxicities section.
- Vaccines that are inactivated or killed preparations are permissible during a course of immunotherapy. Due to the lack of clarity regarding live vaccine use, it is not recommended during ICI therapy.
- Combination therapies with non-ICI agents (eg, vascular endothelial growth factor [VEGF] inhibitors) may complicate irAE workup due to overlapping toxicity. If low suspicion of irAE, consider holding non-ICI therapy and monitoring before use of immunosuppression.
- An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

Principles of Steroid Use in the Management of irAEs

- We recommend early intervention with steroids for the general management of immune-related toxicity.
- If unable to taper steroids, steroid-sparing measures with secondary agents may be appropriate to minimize steroid exposure and expedite resumption of ICI therapy.
- In the absence of specific indications such as prior infusion reaction or concurrent chemotherapy, routine premedication with steroids is not recommended given the potential mitigation of immunotherapeutic effectiveness in the prophylactic setting.
- Steroid Dosing
  - See individual toxicity pages for specific recommendations on steroid dose by grade. Where immunotherapy rechallenge is indicated, see the Principles of Immunotherapy Rechallenge (IMMUNO-C) for guidance by organ site.
  - Higher potency (eg, Class 2 or 3) topical steroids are preferred for short-term use for immune-related dermatitis, compared to longer term use of lower potency steroids.
  - Prednisone is the preferred oral steroid due to ease of dosing and wide availability. IV methylprednisolone is the preferred IV steroid.
- Steroid Taper
  - Longer steroid tapers (>4 weeks, sometimes 6–8 weeks or longer) may be required to prevent recurrent irAE events, particularly pneumonitis, hepatitis, and neuromuscular toxicities.
  - Patients who are initiated on longer steroid tapers should have close follow-up with oncologist or co-managing disease-specific subspecialist team to monitor for side effects of steroid use, and to evaluate any need for modifying immunosuppressant regimen as appropriate based on clinical improvement of irAE.

NCCN Guidelines. Version 1.2026. Management of ICI-Related Toxicities

NCCN Guidelines: Management of ICI-Related Toxicities

- **Prophylaxis**
  - **Infection**
    - ◊ ***Pneumocystis jirovecii*** **pneumonia (PJP) prophylaxis is recommended for patients expected to receive ≥20 mg daily prednisone equivalent for ≥4 weeks. Consider starting PJP prophylaxis if still steroid-dependent by the end of 2 weeks. Sulfamethoxazole-trimethoprim is preferred. For patients with a sulfa allergy, consider aerosolized/IV pentamidine. Consider avoiding atovaquone due to risk of diarrhea particularly in patients with colitis, and avoid dapsone due to risk of hemolytic anemia. Check glucose-6-phosphate dehydrogenase (G6PD) screen prior to dapsone use. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.**
    - ◊ **Other fungal infections are rare, and the utility of prophylaxis for these infections is unclear. Patients receiving extended immunosuppression may be at higher risk of an invasive fungal infection.**
    - ◊ **Prophylaxis against HSV or VZV reactivation can be considered. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.**
  - **Gastritis**
    - ◊ **PPI therapy or H2 blockers can be considered for patients at higher risk of gastritis (eg, NSAID use, anticoagulation) for the duration of steroid therapy. Consider prescribing full-dose PPI when the patient is taking high-dose steroids.**
  - **Osteoporosis**
    - ◊ **If patients need to be on steroids long-term, they are at risk for developing osteoporosis. Vitamin D and calcium supplementation should be provided to prevent osteoporosis. Refer patient to physical therapy and to endocrinology; weight-bearing exercises are recommended.**
    - ◊ **Steroid use of >30 mg for >30 days puts patients at high risk for vertebral fractures. Depending on clinical context, consider use of agents to maintain bone mineral density.**

NCCN Guidelines. Version 1.2026. Management of ICI-Related Toxicities

ASCO Guideline Update: Managing irAEs from ICIs

Key Recommendations

The following are general recommendations that should be followed irrespective of affected organs. For organ-specific and systemic toxicities' management, see Tables 1-11. Note that definitions of grades are found in each table and, for the most part, follow the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.[4]
It is recommended that clinicians manage toxicities as follows:

- Patient and family caregivers should receive timely and up-to-date education about immunotherapies, their mechanism of action, and the clinical profile of possible irAEs before initiating therapy and throughout treatment and survivorship.
- There should be a high level of suspicion that new symptoms are treatment-related.
- In general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, except for some neurologic, hematologic, and cardiac toxicities.
- Consider holding ICPis for most grade 2 toxicities and resume when symptoms and/or laboratory values revert ≤ grade 1. Corticosteroids (initial dose of 0.5-1 mg/kg/d of prednisone or equivalent) may be administered.
- Hold ICPis for grade 3 toxicities and initiate high-dose corticosteroids (prednisone 1-2 mg/kg/d or equivalent). Corticosteroids should be tapered over the course of at least 4-6 weeks. If symptoms do not improve with 48-72 hours of high-dose steroid, infliximab may be offered for some toxicities.
- When symptoms and/or laboratory values revert ≤ grade 1, rechallenging with ICPis may be offered; however, caution is advised, especially in those patients with early-onset irAEs. Dose adjustments are not recommended. Rechallenge with PD-1/PD-L1 monotherapy may be offered in patients with toxicity from combined therapy with a CTLA-4 antagonist once recovered to ≤ grade 1.
- In general, grade 4 toxicities warrant permanent discontinuation of ICPis, except for endocrinopathies that have been controlled by hormone replacement.

All recommendations in this guideline are consensus based with benefits outweighing harms.

Schneider BJ et al. JCO 2021

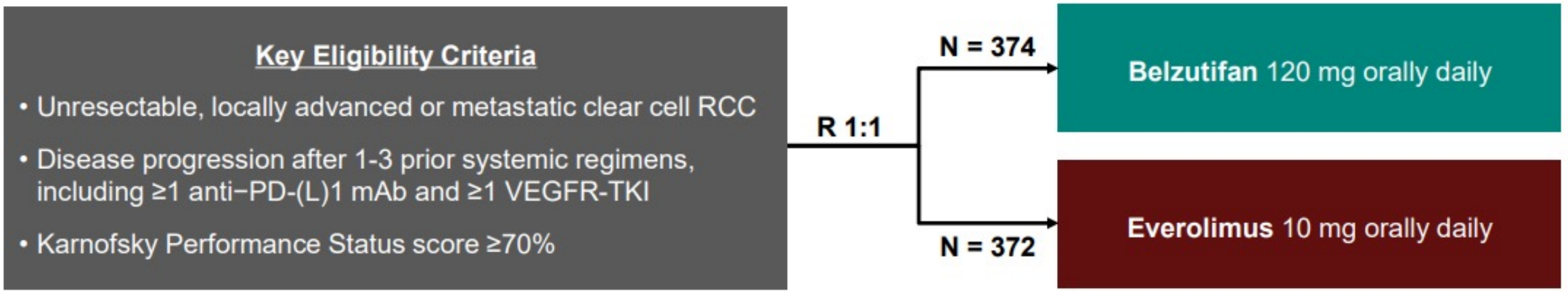
NCCN Guidelines: Management of ICI-Related Toxicities

What about patients with pre-existing autoimmune/viral conditions or organ transplant recipients?

- History of HIV or viral hepatitis? **Possibly**
- Pre-existing autoimmune conditions? **Possibly**
- Organ transplant recipients? **Possibly**
- Prior allogeneic HCT? **Possibly**
- Autoimmune neurologic conditions? **Probably not**
- Life-threatening autoimmune disorders? **Probably not**

NCCN Guidelines. Version 1.2026. Management of ICI-Related Toxicities; Schneider BJ et al. JCO 2021

LITESPARK-005 Study: Design



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

Rini B et al. ESMO 2024

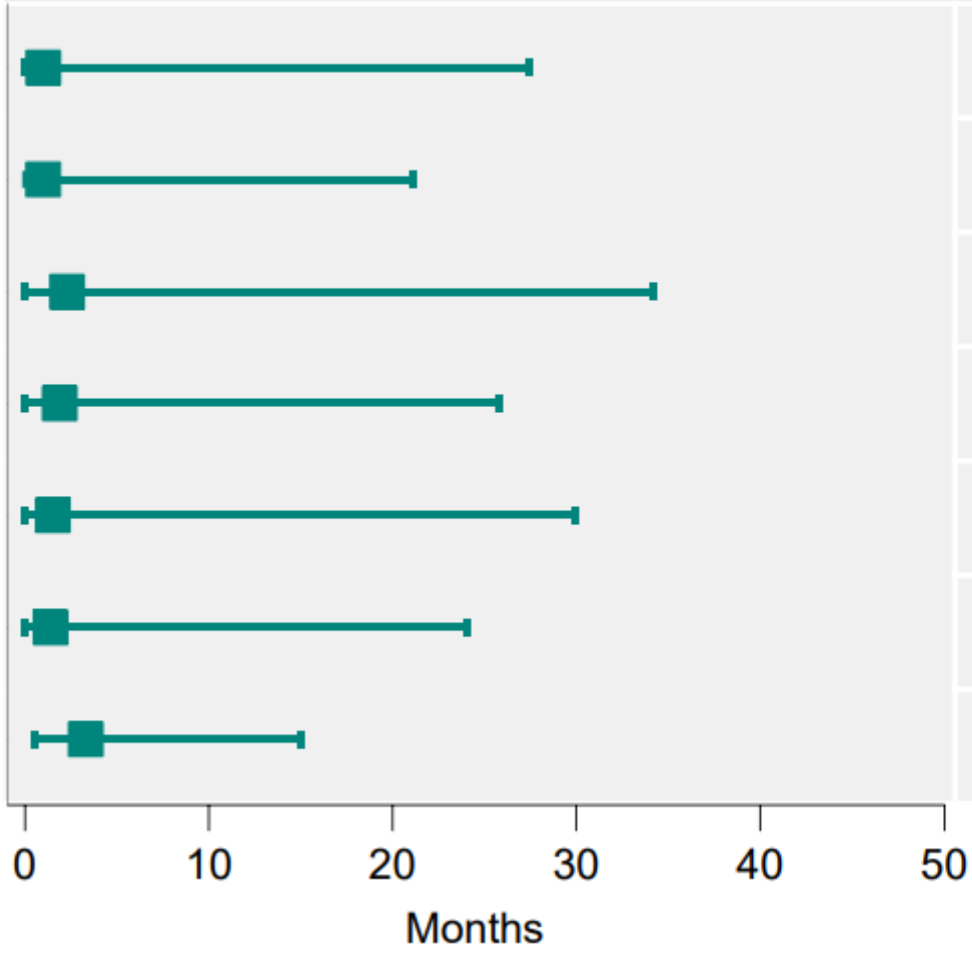
LITESPARK-005 Study: Summary of AEs

	Belzutifan (N = 372)	Everolimus (N = 360)
Median duration of therapy, mo (range)	7.6 (0.1–45.9)	3.9 (0.03–41.8)
All-cause AEs, n (%)	369 (99.2%)	357 (99.2%)
Grade ≥3	234 (62.9%)	226 (62.8%)
Serious	160 (43.0%)	139 (38.6%)
Led to discontinuation	23 (6.2%)	55 (15.3%)
Led to death	14 (3.8%)	19 (5.3%)
Treatment-related AEs, n (%)	333 (89.5%)	322 (89.4%)
Grade ≥3	147 (39.5%)	144 (40.0%)
Serious	49 (13.2%)	48 (13.3%)
Led to death	1 (0.3%)[b]	2 (0.6%)[c]

Rini B et al. ESMO 2024

LITESPARK-005 Study: Time to Onset of Any-Grade AEs

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)



Rini B et al. ESMO 2024

LITESPARK-005 Study: Duration of Any-Grade AEs

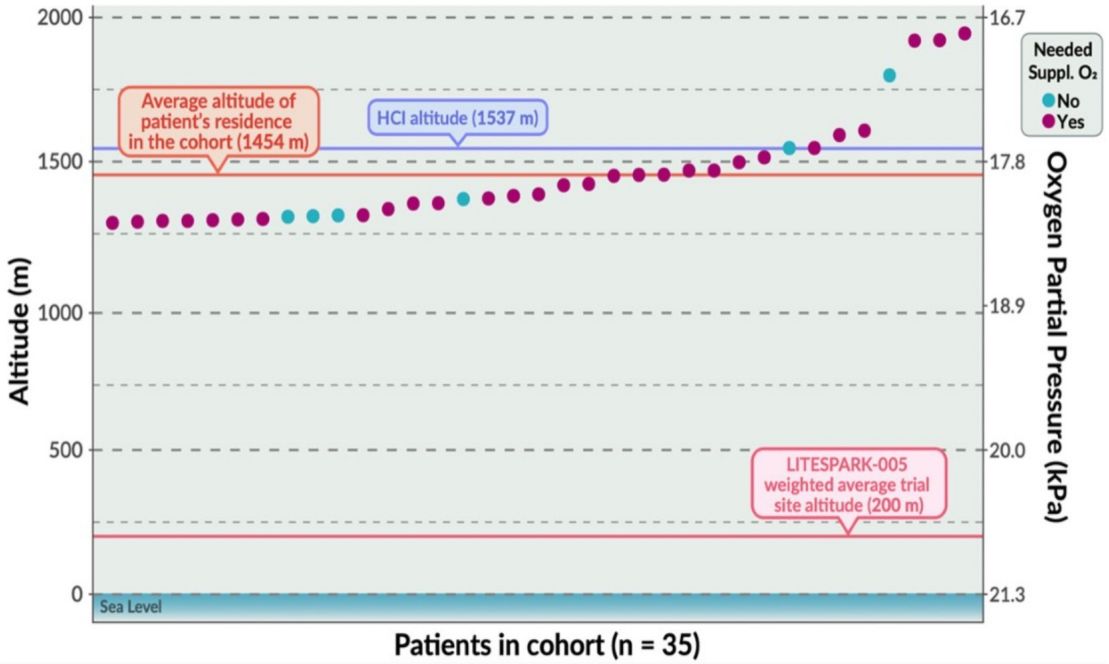
ADR	Incidence, n (%)	Duration, median (range), mo
Anemia	310 (83.3)	4.6 (0.1+–47.1+)
Hypoxia	53 (14.2)	0.5 (0.03–31.9+)
Dizziness	50 (13.4)	1.1 (0.03–35.2)
Dyspnea	57 (15.3)	3.3 (0.03–39.5+)
Fatigue	120 (32.3)	NR (0.1–43.9+)
Nausea	69 (18.5)	1.2 (0.03–38.6)
Weight increased	22 (5.9)	16.6 (0.6–40.0+)

Rini B et al. ESMO 2024

Belzutifan at High Altitudes

Incidence of Symptomatic Hypoxia in a High-Altitude Cohort of Patients with Renal Cell Carcinoma (RCC) Treated with Belzutifan

Figure 1. Average residential altitude for this cohort was 1457m (range: 1288 – 1945m). Oxygen partial pressure was estimated as described in methods.



Adverse Event	Any	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	35 (100%)	8 (23%)	13 (37%)	14 (40%)	-
Hypoxia	31(88%)	2 (6%)	10 (29%)	16 (46%)	3 (9%)

McFarland et al. ASCO GU 2026; Abstract 488.

Belzutifan at High Altitudes

Incidence of Symptomatic Hypoxia in a High-Altitude Cohort of Patients with Renal Cell Carcinoma (RCC) Treated with Belzutifan

Overall, 35 sequential patients with mRCC met eligibility criteria and were included in the analysis. 32 (91%) were male, 29 (83%) were White, 23 (66%) were never smokers, and 23 (66%) had lung metastases at baseline. 3 (10%) were concomitantly treated with a tyrosine kinase inhibitor, and 5 (17%) started at a dose of 200 mg. All had an ECOG of ≤1 and were not on supplemental O_2 prior to start of therapy. The average residential altitude of this cohort was 1457 m (range: 1288 - 1945). Overall, 31 (88%) experienced grade ≥1 hypoxia, with grade 3 being the most common experienced by 16 (46%) patients. At-home supplemental O_2 was required by 28 (82%) and was prescribed at a median of 55.5 days (IQR: 29.3 - 106.5) after starting belzutifan. Grade ≥2 anemia was seen in 27 (79%) patients.

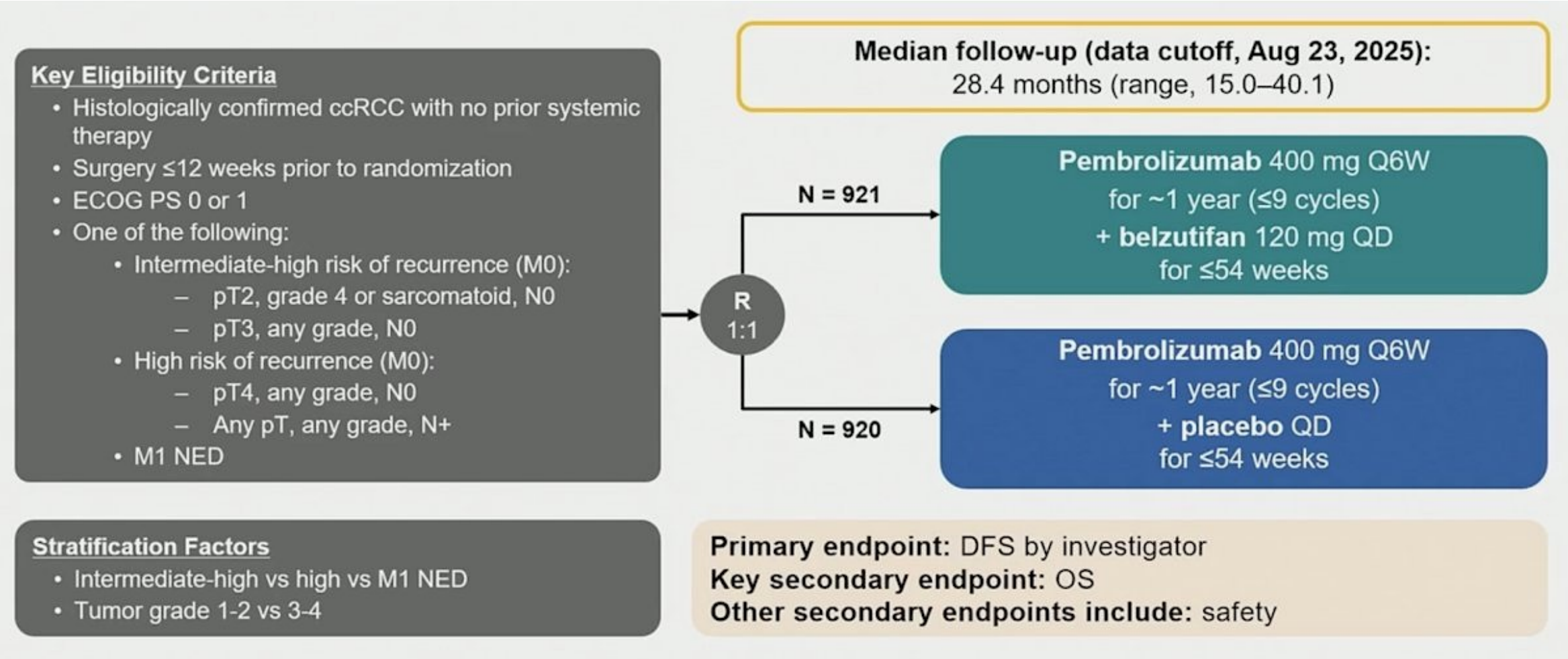
McFarland et al. ASCO GU 2026; Abstract 488.

Managing AEs from Belzutifan

Adverse Reaction	Severity	Dosage Modification
Anemia	Hemoglobin <8 g/dL or transfusion indicated	• Withhold until hemoglobin ≥8g/dL • Resume at the same or reduced dose; or d/c depending on severity of anemia
	Life-threatening or urgent intervention indicated	• Withhold until hemoglobin ≥8g/dL • Resume at a reduced dose or permanently d/c
Hypoxia	Decreased O2 saturation with exercise	• Consider withholding until resolved • Resume at the same dose or at a reduced dose depending on the severity of hypoxia
	Decreased O2 saturation at rest	• Withhold until resolved • Resume at reduced dose or d/c depending on severity of hypoxia
	Life-threatening or recurrent symptomatic hypoxia	• Permanently discontinue
Other adverse reactions	Grade 3	• Withhold dosing until resolved to ≤ G2 • Consider resuming at reduced dose • Permanently d/c upon recurrence of G3
	Grade 4	• Permanently d/c

Belzutifan PI, 2025.

LITESPARK-022 Study: Design



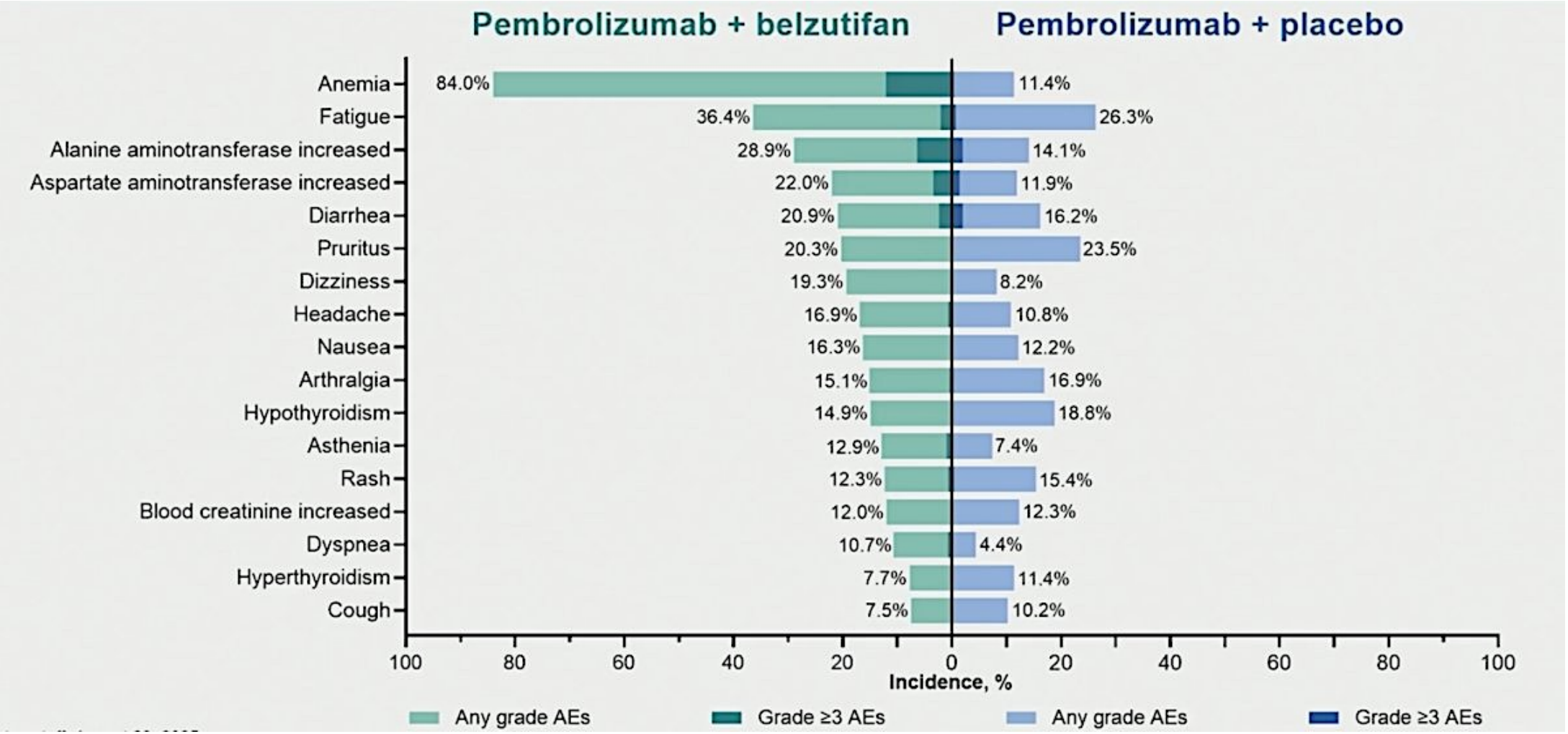
Choueiri TK et al. ASCO GU 2026

LITESPARK-022 Study: irAE and TRAEs leading to discontinuation

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)

Choueiri TK et al. ASCO GU 2026

LITESPARK-022 Study: All Grade AEs



Choueiri TK et al. ASCO GU 2026

LITESPARK-022: Anemia-Related AEs

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)

Choueiri TK et al. ASCO GU 2026

LITESPARK-022: Hypoxia-Related AEs

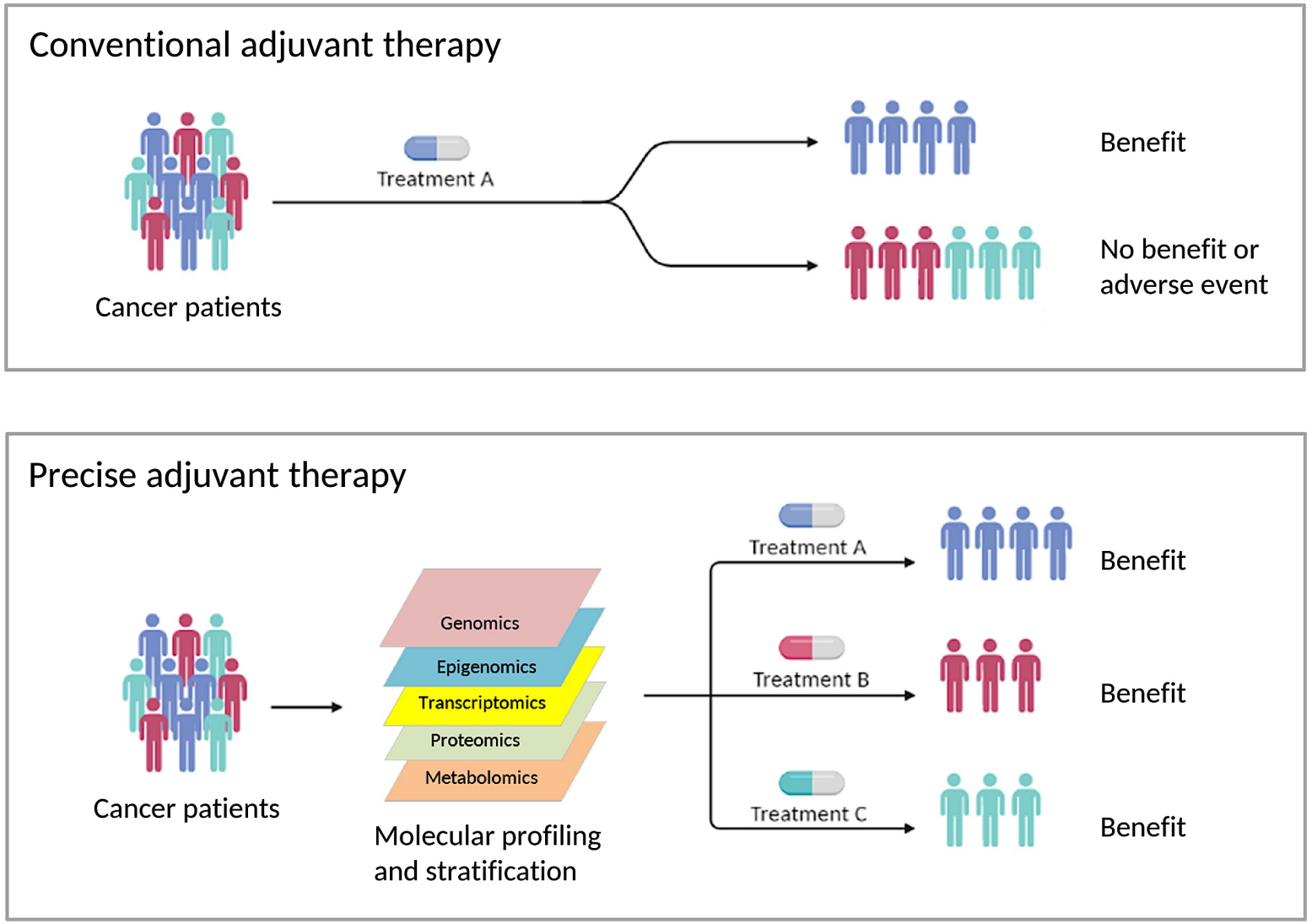
Participants, n (%)	Pembrolizumab + belzutifan (N = 915)	Pembrolizumab + placebo (N = 913)
TEAEs of hypoxia	64 (7.0)	1 (0.1)
Grade ≥3	42 (4.6)	0
Led to interruption of belzutifan/placebo	23 (2.5)	1 (0.1)
Led to dose reduction of belzutifan/placebo	32 (3.5)	0
Led to discontinuation of belzutifan/placebo	15 (1.6)	0
Supportive therapy for hypoxia		
Treated with oxygen therapy	30 (3.3)	0
Median time to onset of oxygen therapy, days (range)	103.5 (16 to 356)	-

Choueiri TK et al. ASCO GU 2026

Core Principles of Adjuvant Therapy

- **Targeting Micrometastatic Disease:** The primary goal is to destroy "hidden" cancer cells that are too small to be seen on scans or during surgery. These cells, if left untreated, can lead to local recurrence or distant metastasis.
- **Risk-Benefit Assessment:** Decisions are tailored to the patient's individual risk profile. Doctors consider the likelihood of recurrence against the potential side effects and impact on the patient's quality of life.
- **Patient Evaluation:** Healthy asymptomatic patient with a long Life expectancy
- **Evidence-Based Selection:** Recommendations are based on rigorous clinical trials that demonstrate improvements in Disease-Free Survival (DFS) or Overall Survival (OS) for specific cancer types and stages.

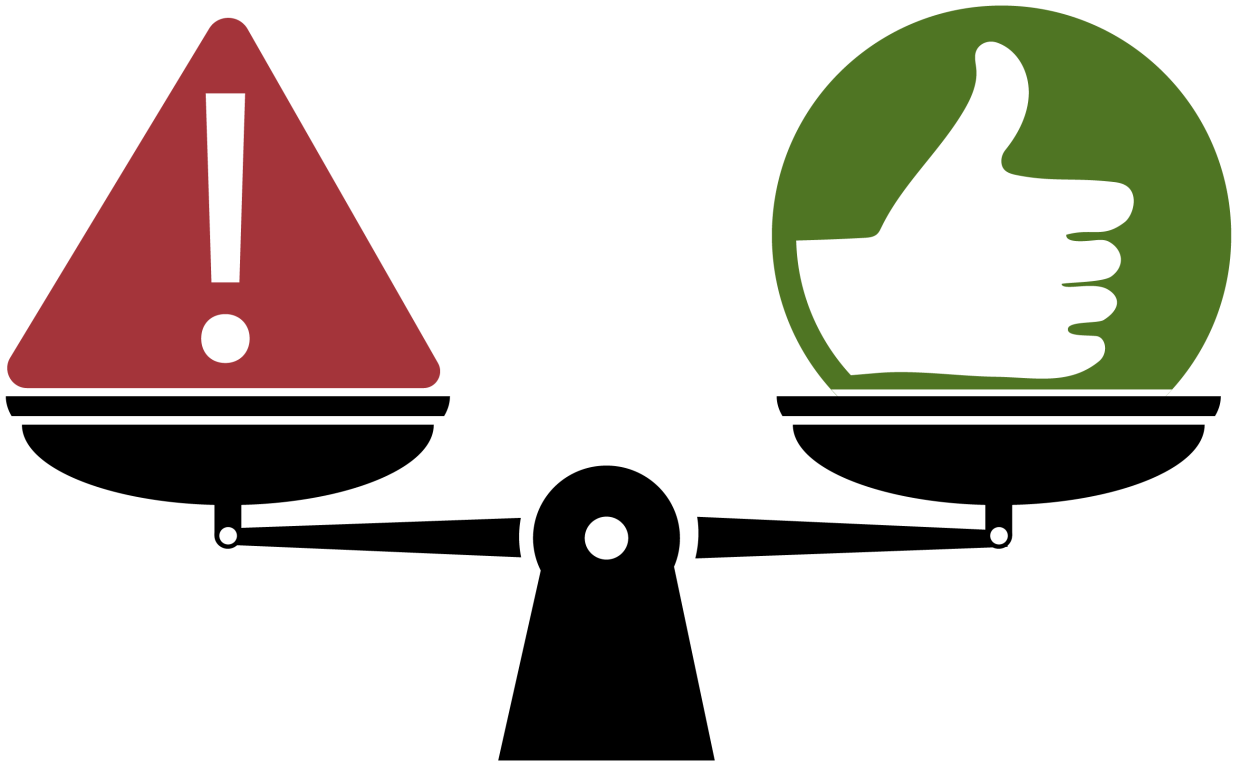
Risk Profiling and Patient selection is Key!



Conclusions: Shared Decision Making

Risks:

1) Severe Anemia- 12%
2) Deaths 1.1%
3) IRAE ≥ grade 3- 8-9%. Can be life long.
4) Cost



Benefits:

1) With pembro +bel: Relapse free survival: 7% increase with belzutifan
   Overall survival: no difference
2) With pembro 9% RFS and 5% OS benefit

Second Opinion

Robert J Motzer, MD

Neil Love, MD

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TO PRACTICE

QUESTIONS FOR THE FACULTY

Do you have any predictions or comments about the ongoing Phase III STRIKE trial evaluating adjuvant pembrolizumab in combination with tivozanib?

How optimistic are you that mRNA-based personalized neoantigen vaccines will play a role in the adjuvant RCC setting in the near future?

Second Opinion

Robert J Motzer, MD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Regulatory and reimbursement issues aside, what is your current preferred second-line treatment for metastatic RCC, and where do you see the combination of lenvatinib/belzutifan fitting in?

Second Opinion: Investigators Provide Perspectives on the Current and Future Management of Prostate Cancer

Part 2 of a 2-Part CME Satellite Symposium Series Held in Conjunction with the 2026 American Urological Association Annual Meeting (AUA2026)

Sunday, May 17, 2026

5:30 PM – 7:30 PM ET

Faculty

Neeraj Agarwal, MD, FASCO
Daniel P Petrylak, MD
Fred Saad, CQ, MD
Neal D Shore, MD

Moderator

Elisabeth I Heath, MD

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