3rd Annual Southern California Genitourinary Cancer Research Forum

Key Updates in Kidney Cancer

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Disclosures

- Consultant for Ambrx, Arcus, AstraZeneca, Aveo, Bayer, Blue Earth Diagnostics, Bristol-Myers Squibb, Calithera, Caris, Daiichi Sankyo, Dendreon, Exelixis, Johnson & Johnson, Lilly, Merck, Myovant, Neomorph, Nimbus, Novartis, Pfizer, Sanofi, SeaGen, Sorrento Therapeutics, Telix, and Tempus

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Diversity aspects of Kidney Cancer Management*
- *Implicit Bias in therapy selection of treatment for patients with kidney cancer*

UC San Diego Health

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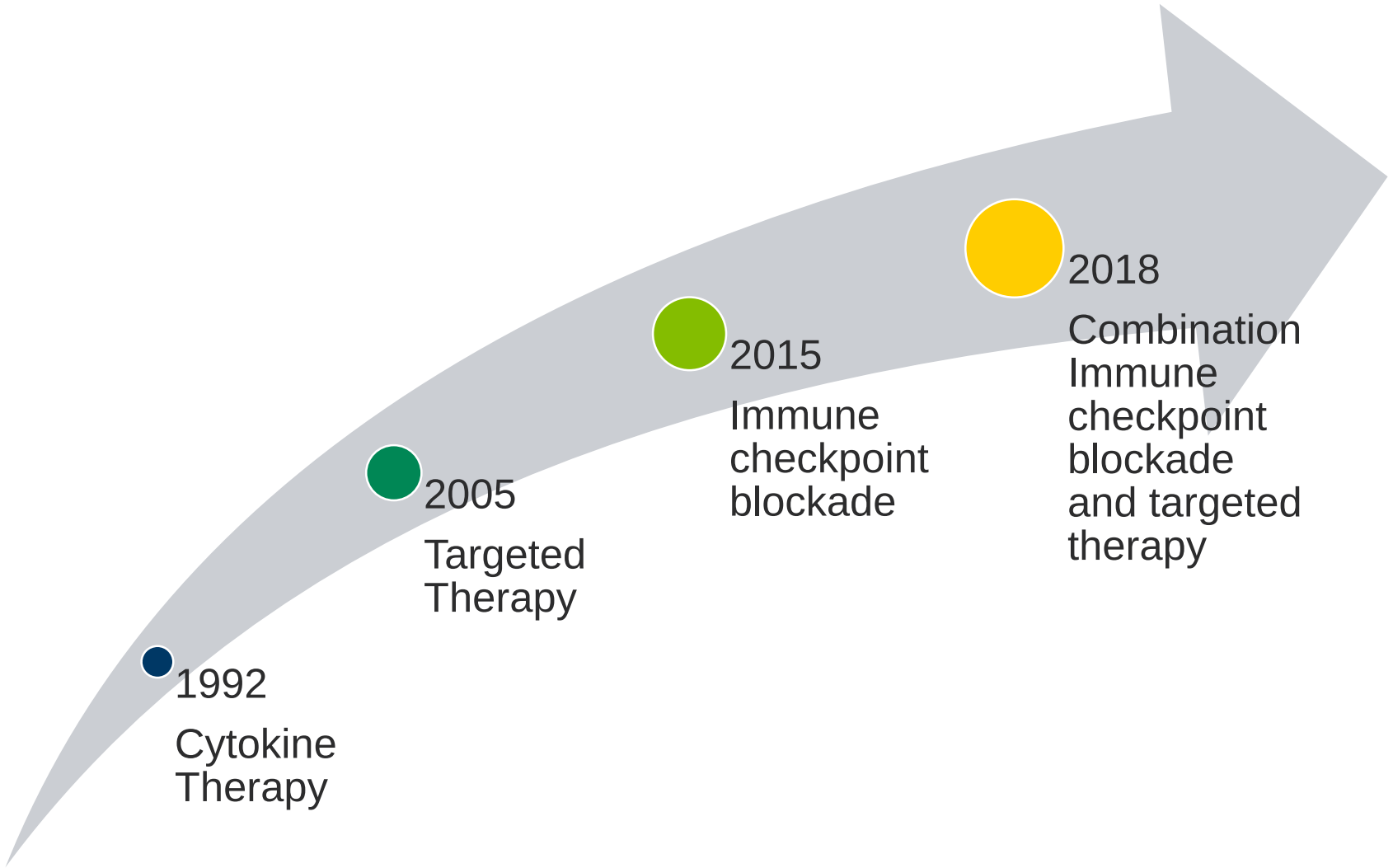
- Consulting or advisory role: Ambrx, Arcus, AstraZeneca, Aveo, Bayer, Blue Earth Diagnostics, Boundless Bio, Bristol Myers Squibb, Calithera, Caris, Dendreon, Daiichi Sankyo, Eli Lilly, Eisai, Exelixis, Janssen, Merck, Myovant, Neomorph, Nimbus, Novartis, Pfizer, Sanofi, SeaGen, Sorrento Therapeutics, Telix, and Tempus.
- Institutional research funding: Artera AI, AstraZeneca, Bayer, Bristol-Myers Squibb, Exelixis, Oncternal, Tempus.

Renaissance of Treatment Options for Renal Cell Carcinoma



The Current Treatment Landscape In RCC

Adjuvant RCC Treatment	Frontline RCC Treatment	Refractory RCC Treatment
Pembrolizumab	Nivolumab + Ipilimumab	Cabozantinib
	Pembrolizumab + Axitinib	Tivozanib
	Nivolumab + Cabozantinib	Belzutifan
	Pembrolizumab + Lenvatinib	Lenvatinib + Everolimus
		Axitinib

Overview

- Updates in the adjuvant setting
- Frontline treatment considerations
- Later line treatment considerations

Adjuvant Pembrolizumab

Key Eligibility Criteria

- Histologically confirmed clear cell renal cell carcinoma
  - **Intermediate-high risk:** pT2, grade 4 or sarcomatoid, N0, M0; pT3, any grade, N0, M0
  - **High risk:** pT4, any grade, N0, M0; any pT, any grade, N+, M0
  - **M1 no evidence of disease (NED)** after surgery[a]
- Surgery ≤12 weeks prior to randomization
- No prior systemic therapy
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment

Stratification Factors

- Metastatic status (M0 vs M1 NED)
- M0 group further stratified:
  - ECOG PS 0 vs 1
  - US vs non-US

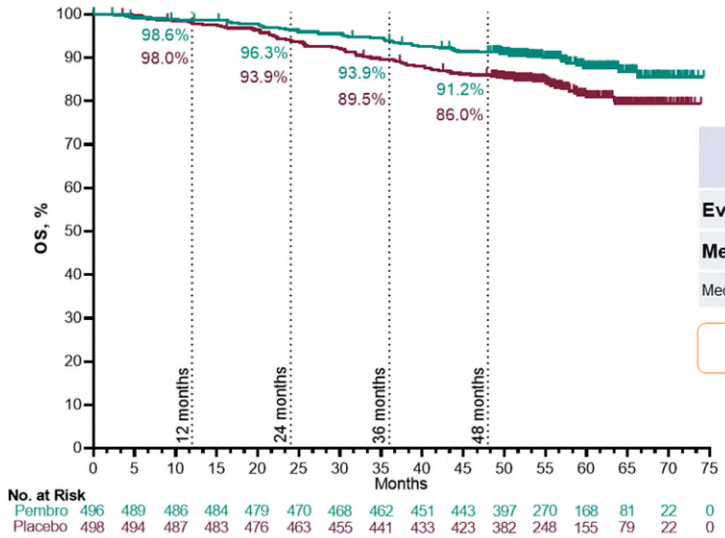
R (1:1)

N = 496 → Pembrolizumab 200 mg Q3W for ~1 year[b]

N = 498 → Placebo Q3W for ~1 year[b]

Primary endpoint: DFS per investigator
Key secondary endpoint: OS
Other secondary endpoints: Safety

Overall Survival



	Pembro (N = 496)	Placebo (N = 498)
Events, n	55	86
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)

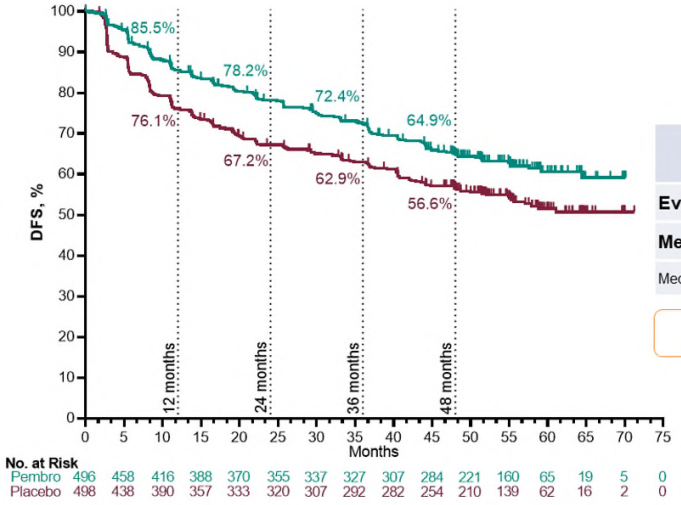
Median follow-up was 57.2 months (range, 47.9–74.5)

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.

Disease Free Survival



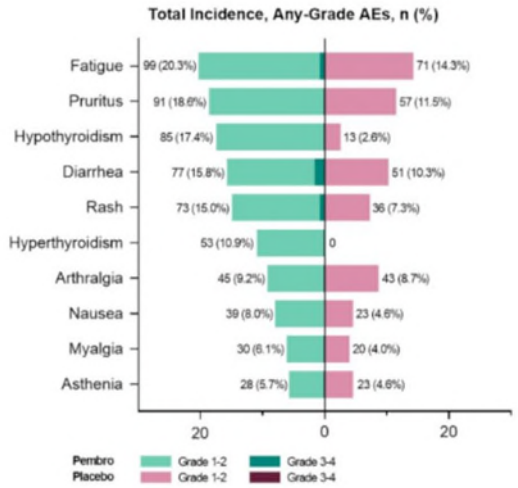
	Pembro (N = 496)	Placebo (N = 498)
Events, n	174	224
Median, mo (95% CI)	NR (NR–NR)	NR (54.9–NR)

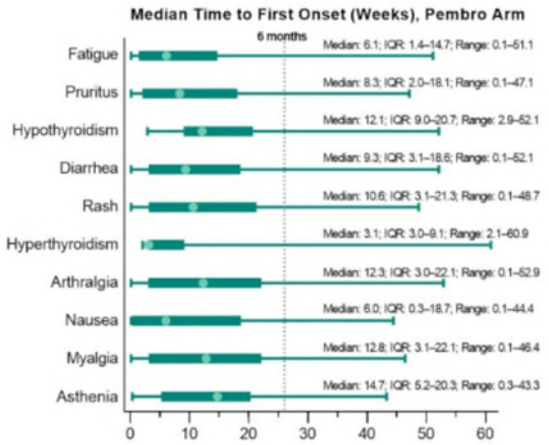
Median follow-up was 57.2 months (range, 47.9–74.5)

HR 0.72 (95% CI 0.59–0.87)

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

Data cutoff date: September 15, 2023.

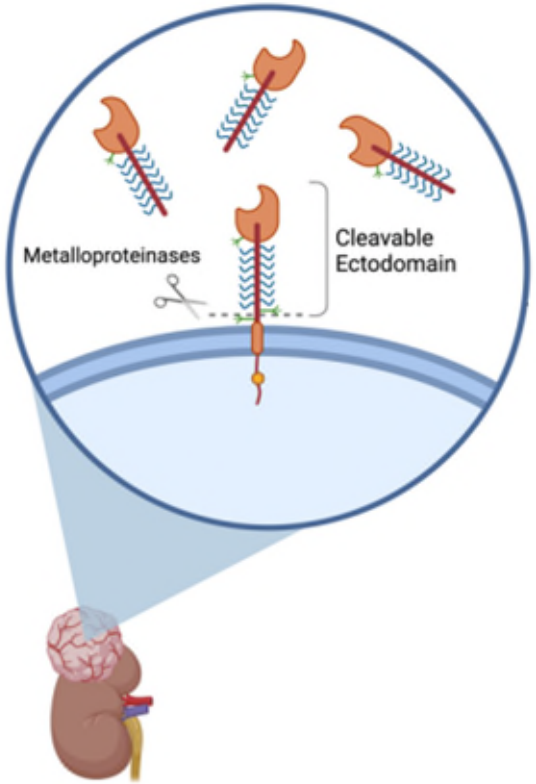




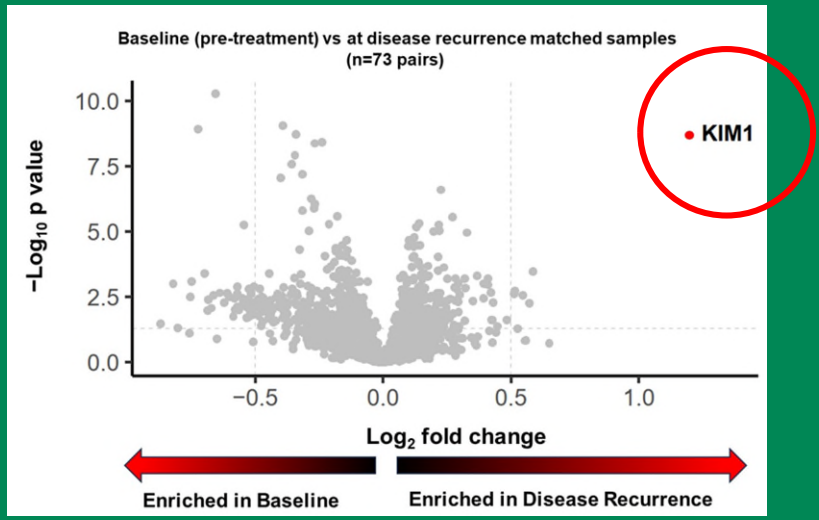
Choueiri, GU ASCO, 2022

What is Kidney Injury Molecule-1?

- Transmembrane glycoprotein that is overexpressed in clear cell and papillary RCC
- Its extracellular domain has been previously identified as a circulating biomarker in kidney injury and RCC diagnostic arenas



A high-throughput protein analysis assay (Olink Explore) compared protein levels in 61 cancer patients at recurrence versus baseline. Of 2,925 proteins tested, circulating KIM-1 showed the greatest increase at recurrence.



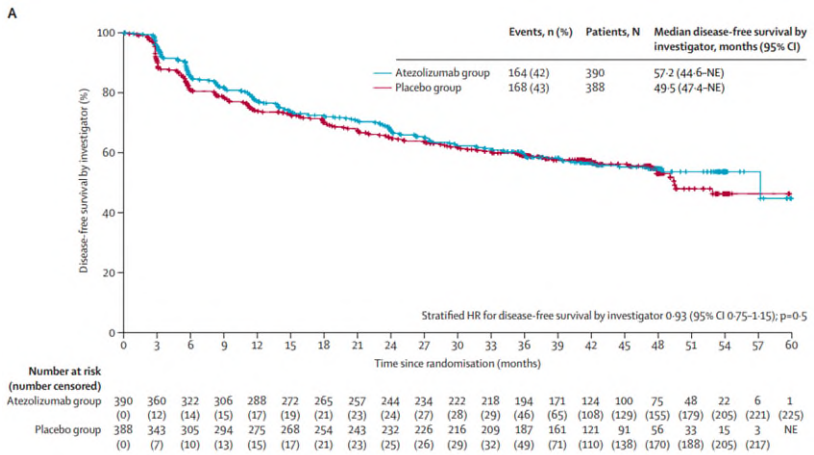
RCC=Renal cell carcinoma; KIM-1=Kidney injury molecule 1.

Albiges et al, GU ASCO, 2025; Rini et al, Ann Oncol, 2025

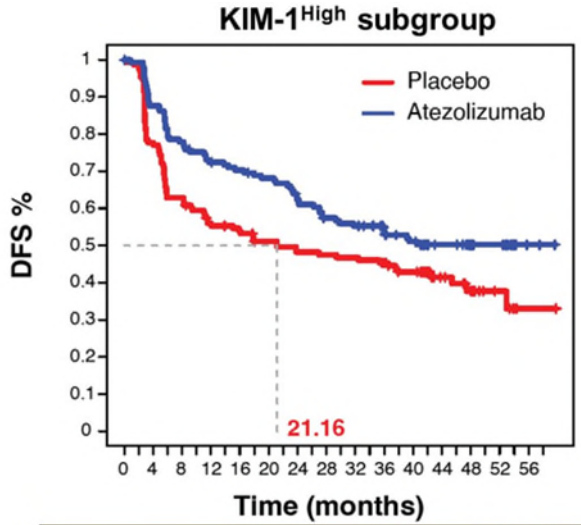
Predictive Value of KIM-1 in Renal Cell Carcinoma

Phase 3 IMmotion010 Adjuvant Trial

Primary Endpoint
Intent to Treat Population – DFS
No Improvement in DFS

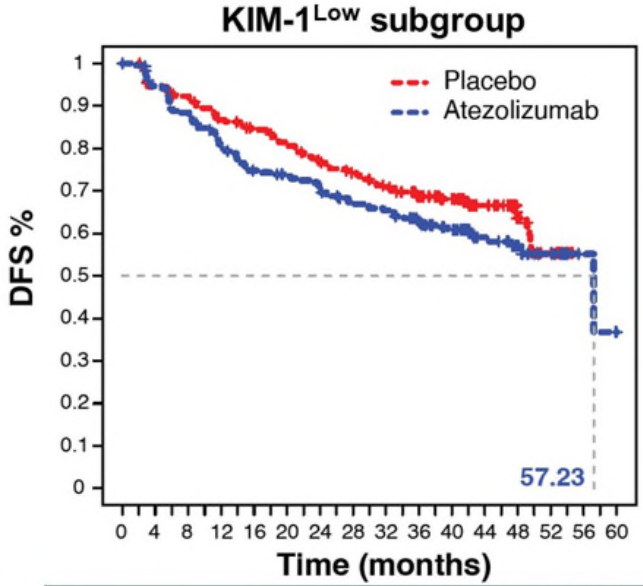


Exploratory Analysis
KIM-1 Evaluable Population – DFS
Improved DFS in KIM-1 High



	n	Median DFS	HR[a] (95% CI)
Atezolizumab	151	NE	0.72 (0.52, 0.99)
Placebo	149	21.16	

Exploratory Analysis
KIM-1 Evaluable Population – DFS
No Difference in DFS in KIM-1 Low



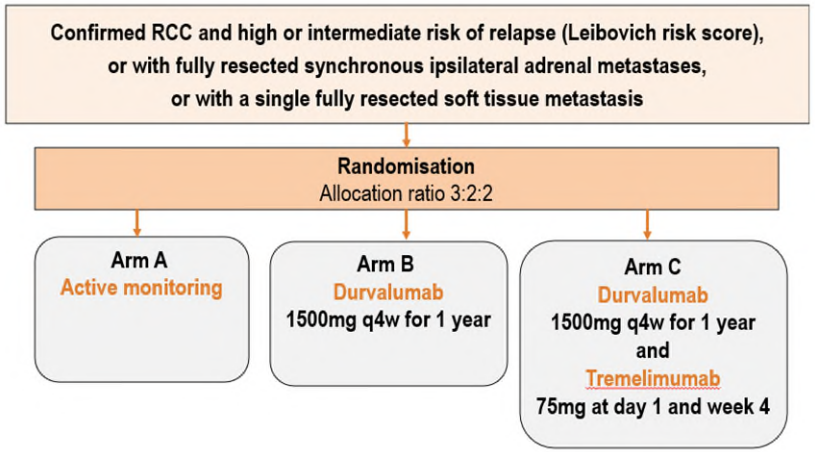
	n	Median DFS	HR[a] (95% CI)
Atezolizumab	229	57.23	1.12 (0.88, 1.63)
Placebo	223	NE	

97% (n=752/778) KIM-1 evaluable
40% KIM-1 High at baseline

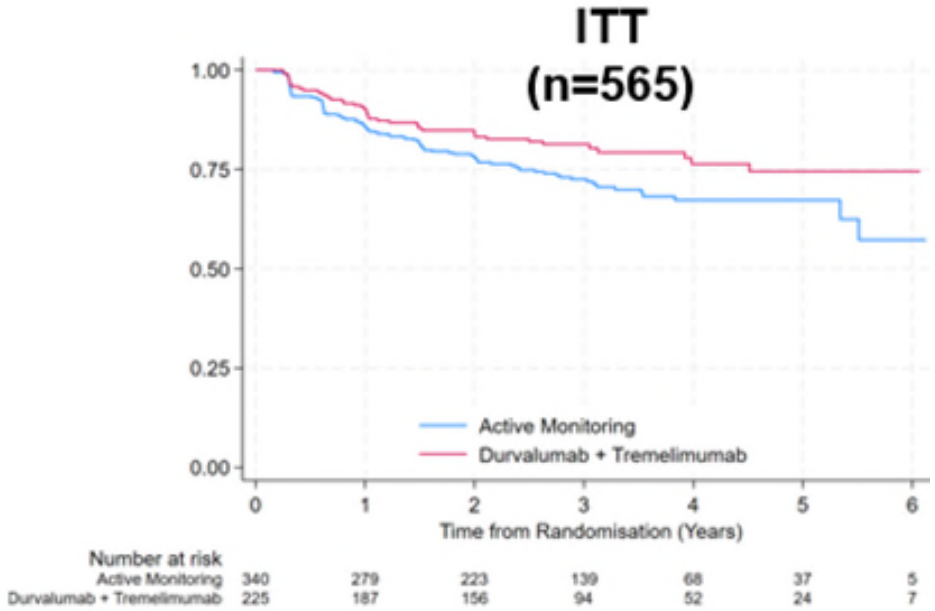
KIM-1=Kidney injury molecule 1; DFS=Disease free survival.

Albiges et al, GU ASCO, 2025; Rini et al, Ann Oncol, 2025

RAMPART – Positive DFS but at a Cost



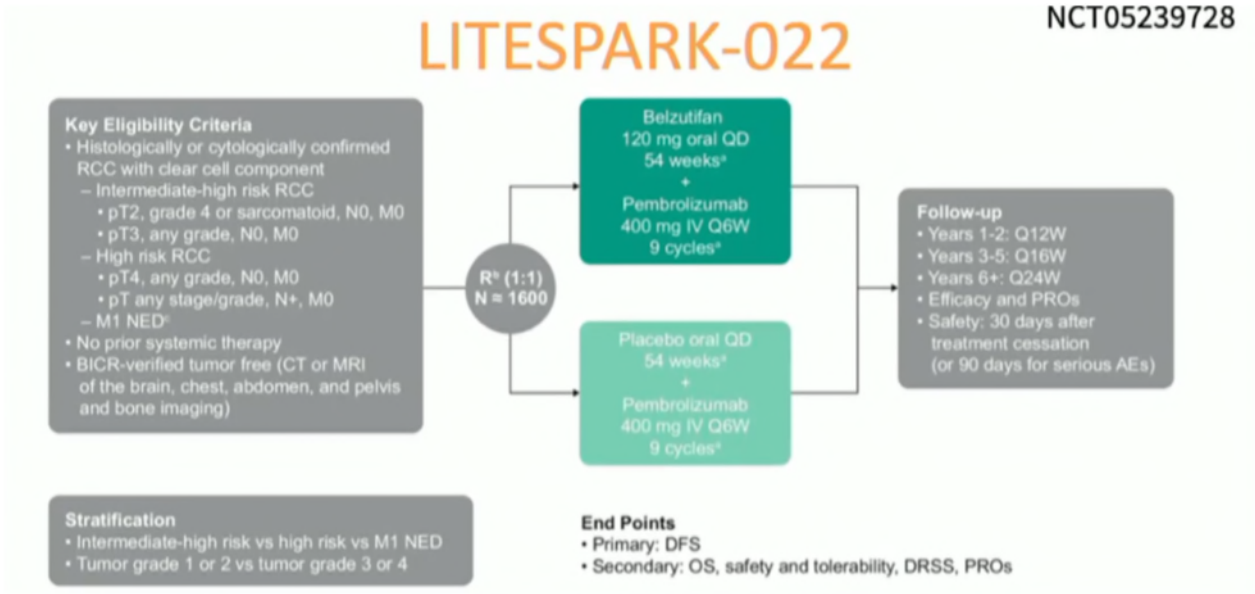
	Active Monitoring (N= 340)	Durvalumab + Tremelimumab (N= 207)
Any-grade AE, any cause, N(%)	**213 (63%)**	**201 (97%)**
Immune related	2 (<1)	137 (66%)
Durvalumab related	-	185 (89%)
Tremelimumab related	-	164 (79%)
Grade ≥ 3 AE, any cause, N(%)	**28 (8%)**	**83 (40%)**
Immune related	-	63 (30%)
Durvalumab related	-	80 (39%)
Tremelimumab related	-	72 (35%)
Any-grade SAE, any cause, N(%)	**20 (6%)**	**70 (34%)**
Durvalumab related	-	51 (25%)
Tremelimumab related	-	49 (24%)
Deaths	**15 (4%)**	**9 (4%)**
Treatment related	-	2* (<1%)
AE leading to treatment discontinuation, N(%)	-	**66 (32%)****
Durvalumab	-	59 (29%)
Tremelimumab	-	30 (14%)



3-year DFS (95% CI)	
D + T (N=225)	**Monitoring (N=340)**
81% (75%, 86%)	73% (67%, 77%)
Median Follow Up (IQR), years: 3.03 (2.33, 4.05)	
HR (95% CI) 0.65 (0.45, 0.93), one-sided P= 0.0094	

Larkin et al, ESMO, 2025

LiteSpark-022 Reinforces Support for Adjuvant



Company statements > Media > News release

Merck Announces KEYTRUDA® (pembrolizumab) Plus WELIREG® (belzutifan) Met Primary Endpoint of Disease-Free Survival (DFS) in Certain Patients With Clear Cell Renal Cell Carcinoma (RCC) Following Nephrectomy

Save

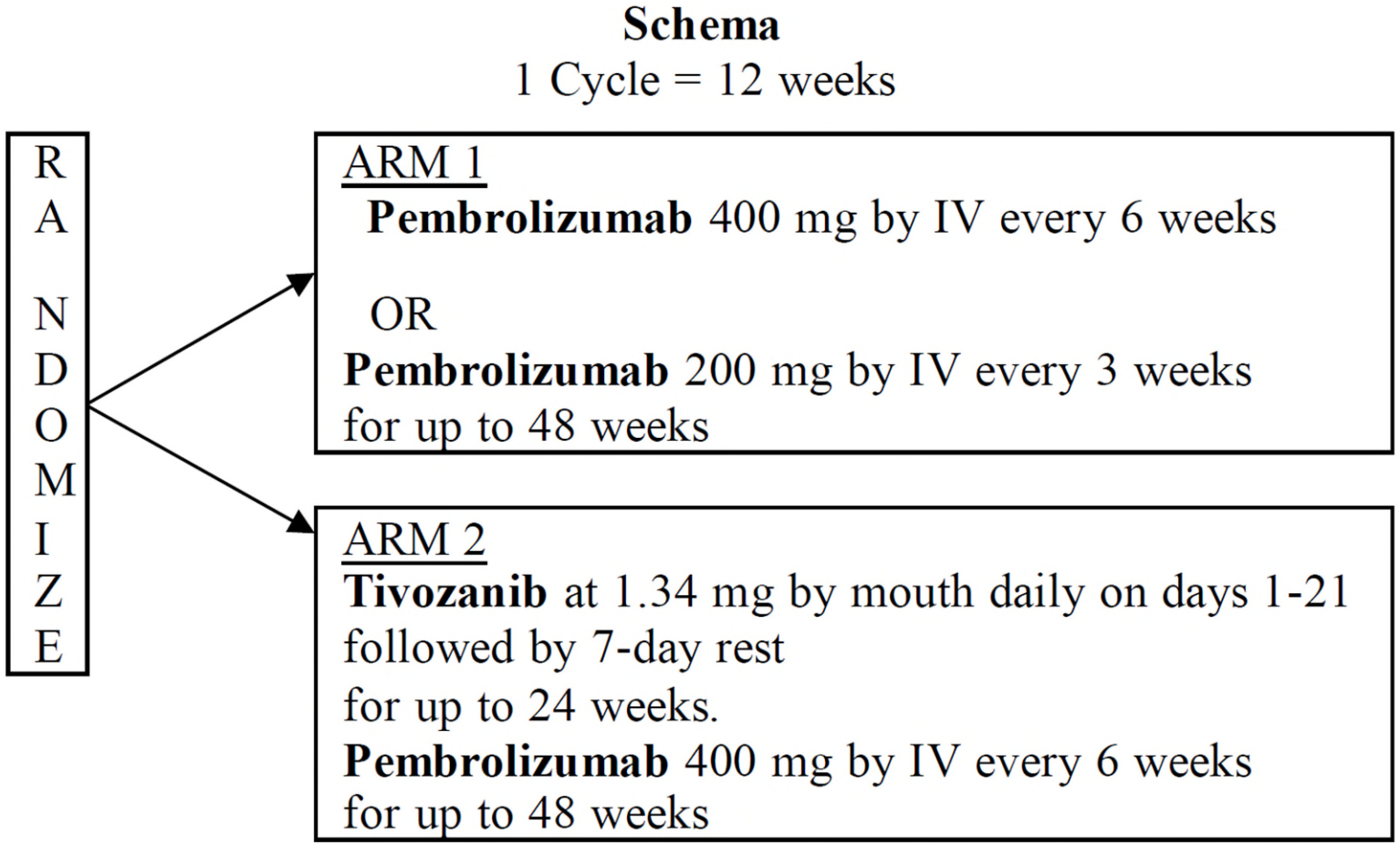
October 28, 2025 6:45 am EDT

First combination regimen to demonstrate improvement in DFS compared to KEYTRUDA monotherapy for these patients in the adjuvant setting

LITESPARK-022 is the second positive Phase 3 study for WELIREG as part of a combination regimen in RCC

RAHWAY, N.J.,--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced positive topline results from the Phase 3 LITESPARK-022 trial in patients with clear cell renal cell carcinoma (RCC) following nephrectomy. In this study, KEYTRUDA® (pembrolizumab), Merck's anti-PD-1 therapy, in combination with WELIREG® (belzutifan), Merck's first-in-class, oral hypoxia-inducible factor-2 alpha (HIF-2α)

STRIKE – Actively Accruing



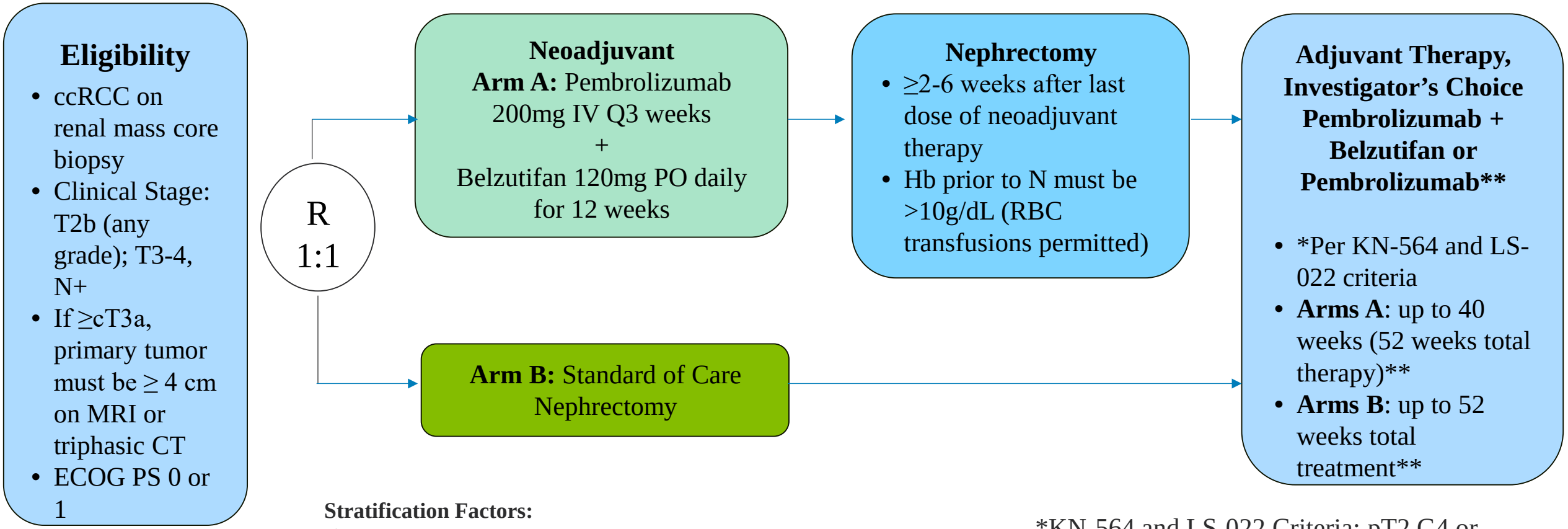
Neoadjuvant/Perioperative Studies of CPI

Trial	Design	N	Study Population	Treatment	Primary Endpoint	RFS/DFS/MFS
Carlo et al	P2, Single	18	12-year probability of metastases of ≥20%, Clear Cell	Nivolumab x 4 cycles	Feasibility / Safety	**RFS 1-year 82%**
Gorin el al	P2, Single	17	cT2a-T4NxM0 or cTxN1M0, Clear Cell	Nivolumab x 3 cycles	Safety	**MFS 3-year 85.1%**
NeoAvAx	P2, Single	40	cT1b-T2aG4N0M0, cT2b-T3aG3–4N0M0, cT3b-T4GxN0M0, cxN1GxM0, Clear Cell	Avelumab + Axitinib x 12 weeks	RECIST ORR	**Median DFS NR, recurrence 32.5%**
Karam et al	P2, Single	20	cT2-T3bN0M0, Clear Cell	Sitravatinib → Sitravatinib + Nivolumab x 4-6 weeks	ORR	**Median DFS NR, 24-month DFS 88%**
Prosper (Allaf et al, Lancet, 2024)	P3	819	≥T2Nx, TxN1, TxNxM1 (resected to NED); any histology	Nivolumab vs. observation x 1 year	EFS	**0.94 95% CI 0.74-1.21**

Evidence for neoadjuvant therapy in RCC remains limited to small, single-arm phase 2 studies with heterogeneous populations and varying endpoints, making definitive conclusions difficult

CPI=Checkpoint inhibitor; P=Phase; RFS=Recurrence-free survival; DFS=Disease free survival; MFS=Metastasis-free survival; NR=Not reached; NED=No evidence of disease; EFS=Event-free survival; RCC=Renal cell carcinoma.

NEOSHIFT – A032503 Schema



Stratification Factors:
1) ECOG PS: 0 vs 1
2) Disease stage: cT2b N0/Nx RCC versus ≥cT3 N0/Nx RCC versus cTany N+ RCC

*KN-564 and LS-022 Criteria: pT2 G4 or sarcomatoid; pT3/4 any grade N0, any pT, any grade, N+; (M1 NED patients are not permitted)
** Must start within 84 days of nephrectomy

Frontline RCC IO Combinations

	Nivolumab + Ipilimumab CheckMate-214 n=1096	Pembrolizumab + Axitinib Keynote 426 n=861	Nivolumab + Cabozantinib CheckMate-9ER n=651	Pembrolizumab + Lenvatinib Clear n=1096
Follow-up, mo	99.1 (median)	67.2 (median)	55.6 (median)	49.8 (median)
Median PFS, mo	12.4	15.7	16.4	23.9
PFS HR	0.88	0.69	0.58	0.47
Landmark PFS	90-month 21%	60-month 18%	48-month 17%	36-month 37%
Median OS, mo	52.7	47.2	46.5	53.7
Landmark OS	90-month 35%	60-month 42%	48-month 49%	36-month 66%
OS HR	0.72	0.84	0.77	0.79
ORR, %	39	61	57	71
CR, %	12	12	14	18
PD, %	18	12	7	5
Quality of Life	Improved	Similar	Improved	Similar-Improved

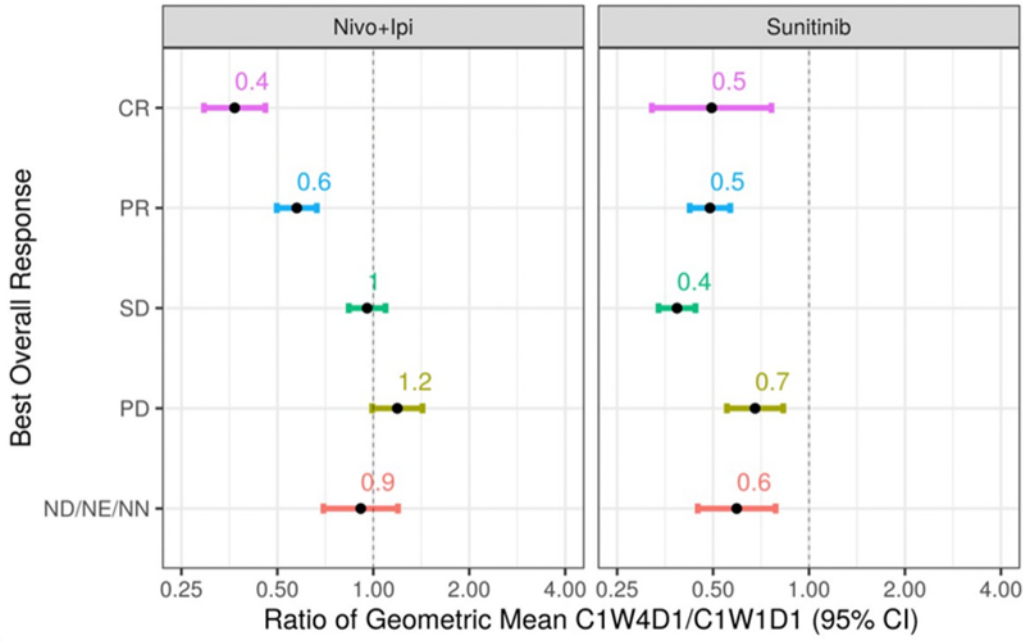
Predictive Value of KIM-1 in Renal Cell Carcinoma

Phase 3 CheckMate 214 Trial

3 wks KIM-1 change	N (%)	ORR, % (95% CI)	mPFS, months	mOS, months
>30% Decrease	140 (31.7)	69.3 (60.9-76.8)	70.8 (17.8- NR)	85.4 (63.1-NR)
>10-30% Decrease	87 (19.7)	36.8 (26.4-47.8)	11.4 (6.3-18.2)	66.1 (40.4-80.1)
<10% Change	86 (19.5)	30.2 (20.8-41.1)	15.4 (10.3-20.7)	52.7 (30.3-70.7)
>10-30% Increase	56 (12.7)	23.2 (13.0-36.4)	7.1 (4.2-16.8)	40.3 (23.8-58.4)
>30% Increase	72 (16.3)	13.9 (6.9-24.1)	4.2 (3.0-8.1)	26.6 (18.8-38.4)

Increase in KIM-1 at 3 weeks identifies non-responders to Nivolumab + Ipilimumab

Decrease in KIM-1 at 3 weeks strongly predictive of radiographic response in nivolumab + ipilimumab arm but not sunitinib arm



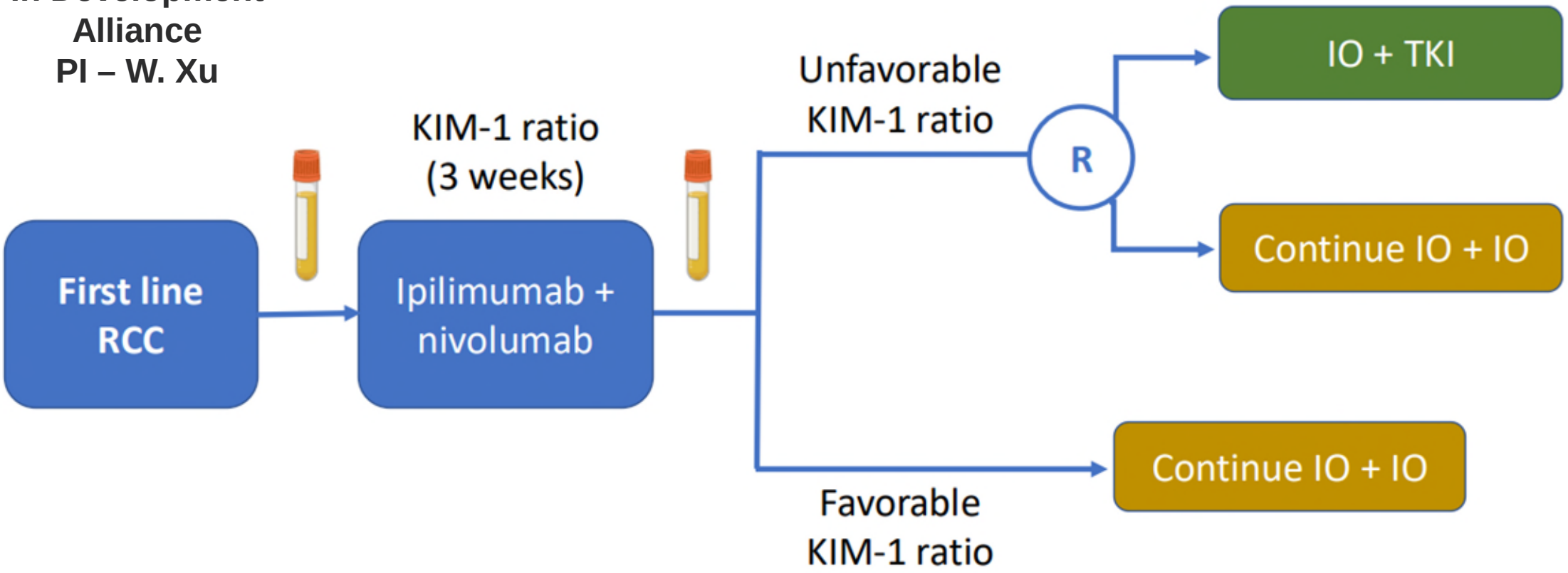
75% (n=821) KIM-1 evaluable

KIM-1=Kidney injury molecule 1.

Xu et al, GU ASCO, 2025

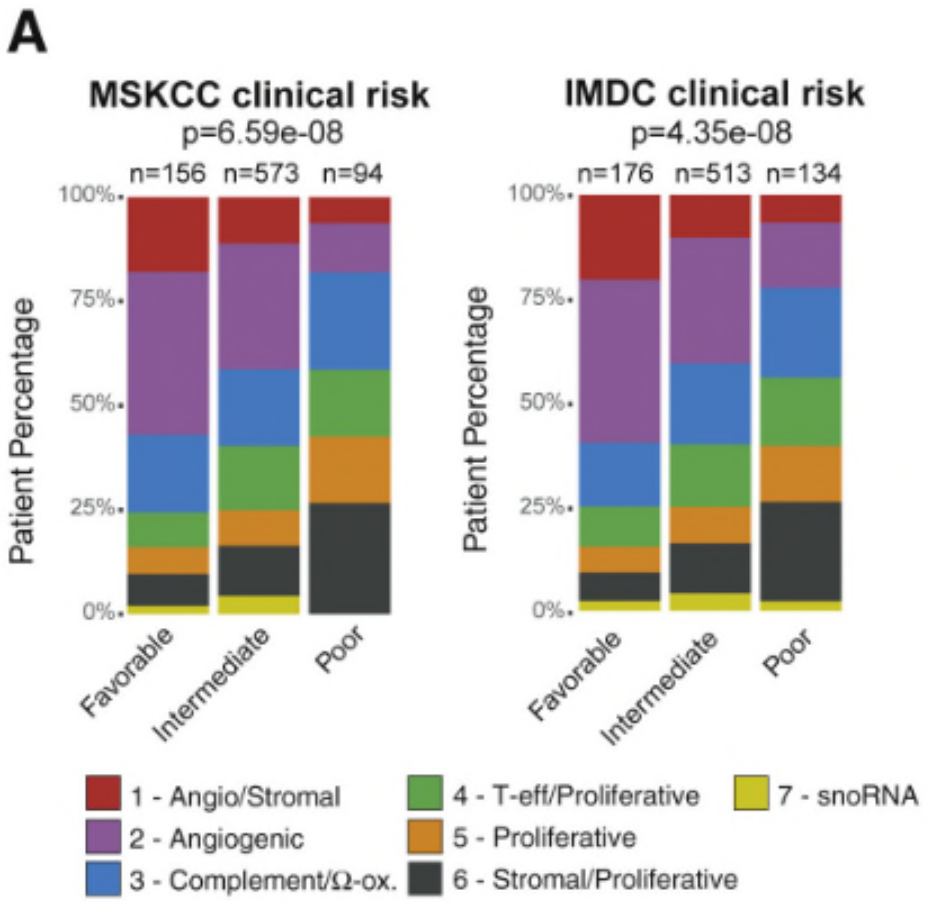
KIMERA – Optimizing Nivolumab + Ipilimumab Use

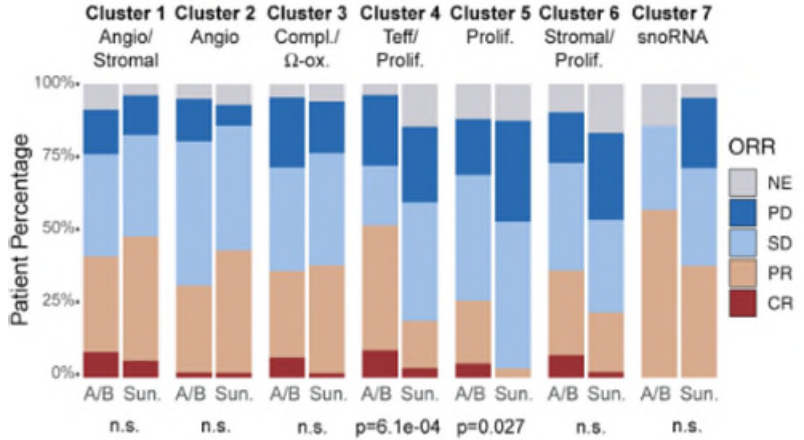
In Development
Alliance
PI – W. Xu



RCC=Renal cell carcinoma; KIM-1=Kidney injury molecule 1; IO=Immuno-oncology; TKI= Tyrosine kinase inhibitor.

Personalized Therapy Strategies: Predictive Gene Signatures





Cluster	PFS HR (95% CI)	p-value	A/B mPFS	Sunitinib mPFS
1 - Angio/stromal	1.11 (0.65−1.88)	0.708	15.3	13.9
2 - Angiogenic	1.16 (0.82−1.63)	0.397	13.8	14.2
3 - Complement/Ω-ox.	0.92 (0.63−1.34)	0.666	8.1	7.1
4 - T-eff/Proliferative	0.52 (0.33−0.82)	0.005	10.9	6.1
5 - Proliferative	0.47 (0.27−0.82)	0.007	8.3	4.3
6 - Stromal/Proliferative	0.81 (0.52−1.25)	0.331	6.8	5.2
7 - snoRNA	0.10 (0.01−0.77)	0.028	NR	7.4

Motzer et al, Cancer Cell, 2020

On the Horizon: Biomarker Driven Optic Trial

Phase II, open-label, parallel single-arm study using tumor RNAseq cluster to assign protocol treatment

PI: Brian Rini, MD

Eligibility
- ECOG 0 or 1
- Newly diagnosed metastatic clear-cell renal cell carcinoma
- No prior systemic therapy
- Available tumor tissue for RNA-sequencing/cluster prediction
- Patients with clusters 3/6 will be excluded

Primary Endpoint:
-ORR per RECIST
Secondary Endpoints:
-PFS
-Depth of response >80% at 6 months.

Clusters 1/2 → Simon's MinMax Two-Stage Design → **Nivolumab/Cabozantinib (N=26)**

- H_0: ORR ≤ 55%
- H_A: ORR > 75%

Stage I (N=12) ≥7/12 responders → **Stage II (N=14)** ≥18/26 responders

Clusters 4/5/7 → Simon's MinMax Two-Stage Design → **Ipilimumab/Nivolumab (N=28)**

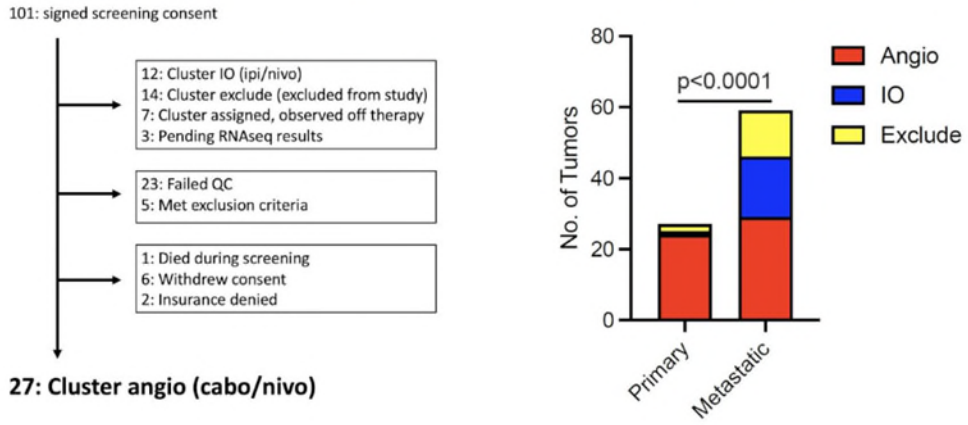
- H_0: ORR ≤ 40%
- H_A: ORR > 60%

Stage I (N=16) ≥7/16 responders → **Stage II (N=12)** ≥15/28 responders

Principal Investigator: Brian Rini

OPTIC – Outcomes of Angio Cluster

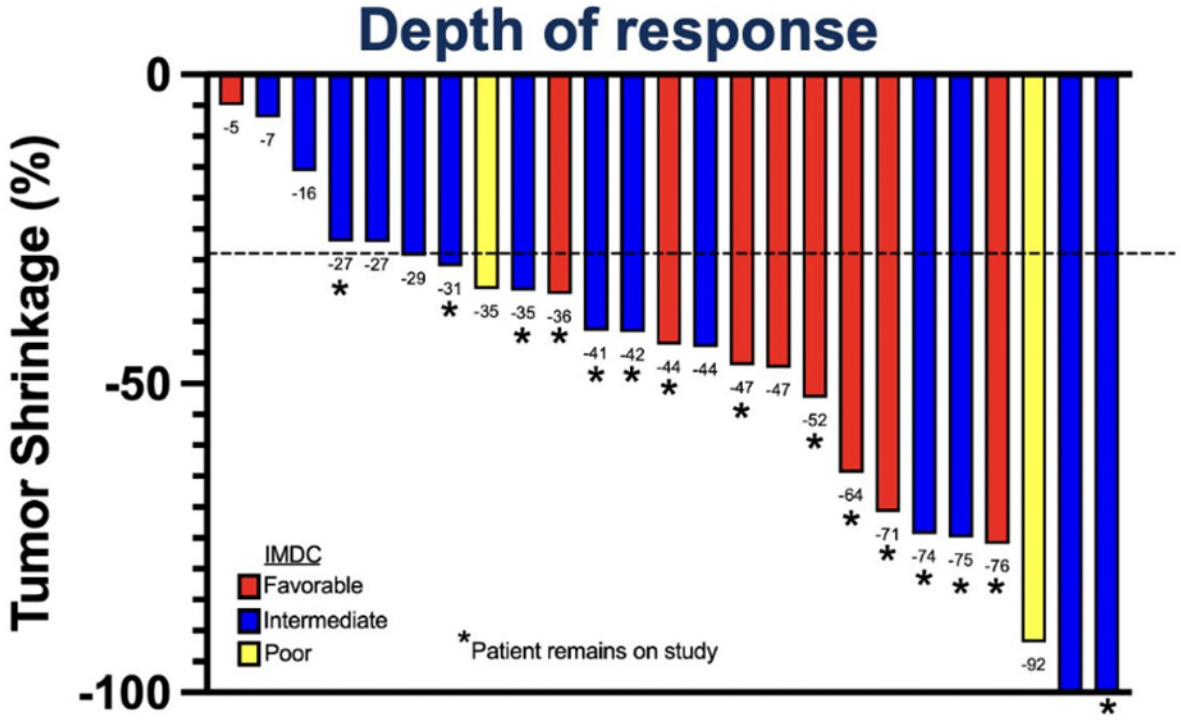
CONSORT diagram & cluster distribution



Objective Response

	Cluster 1/2 (n=25)*
Objective response – no. (%)	19 (76)
Best overall response – no. (%)	
Complete response	2 (8)
Partial response	17 (68)
Stable disease	6 (24)
Progressive disease	0 (0)
Patients with tumor burden reduction – no. (%)	25 (100)
% tumor shrinkage – median (range)	42 (5-100)

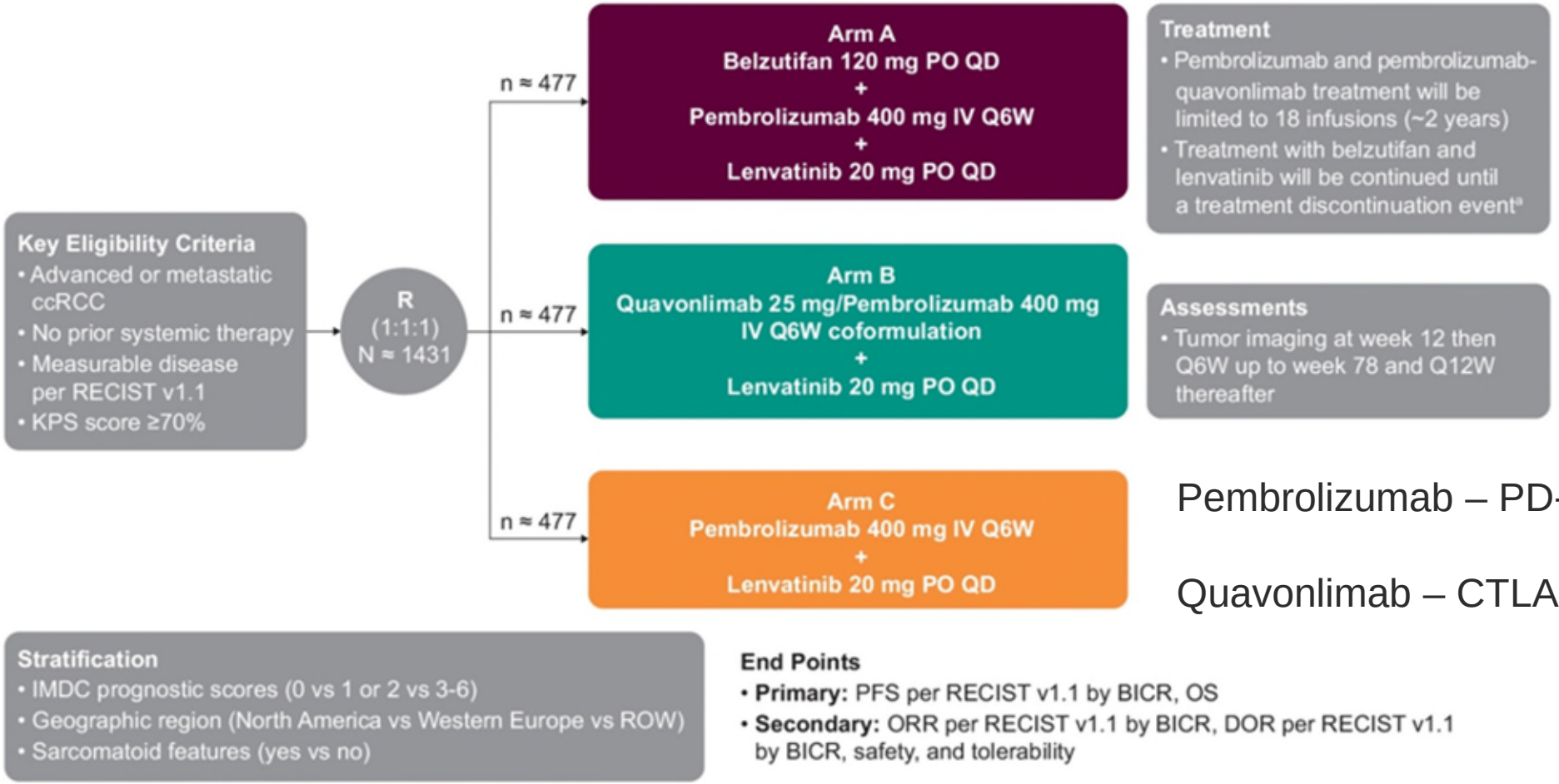
Depth of response



Haake, ESMO, 2025

On the Horizon: Additional Triple Therapy Combinations

MK6482-012

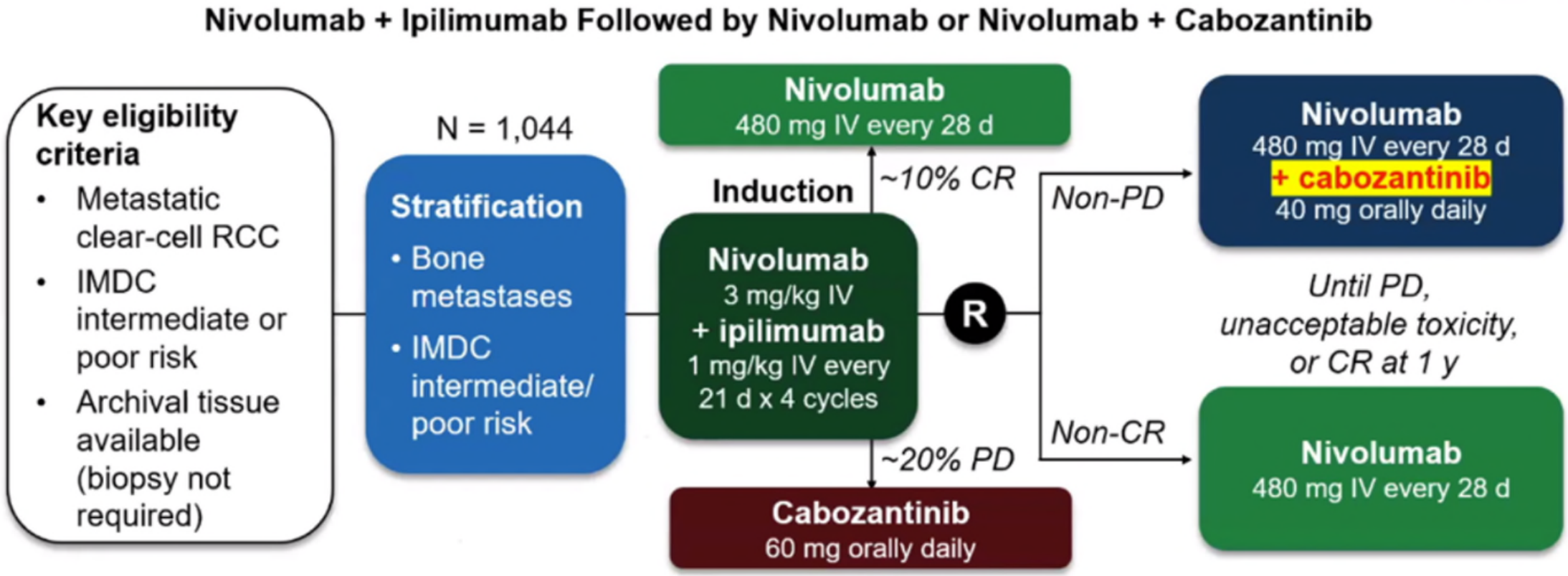


Pembrolizumab – PD-1 inhibitor

Quavonlimab – CTLA-4 inhibitor

On the Horizon: Maintenance IO-VEGF

PDIGREE (Alliance A031704) Schema



Endpoints

- **Primary:** OS
- **Key secondary:** PFS, 1-y CR rate, ORR by RECIST, toxicity, and correlatives

Principal Investigator: Tian Zhang

Renaissance of Radiotherapy in RCC

SABR – Highly focused radiation that gives an intense dose of radiation concentrated on a tumor, while limiting the dose to the surrounding organs

A REVIEW OF HUMAN CELL RADIOSENSITIVITY *IN VITRO*

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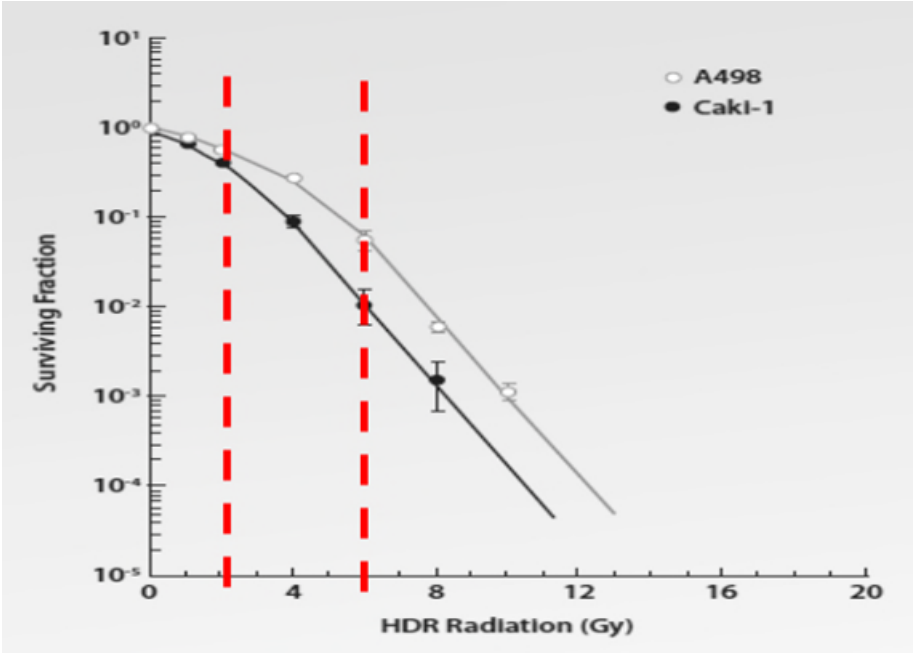
The survival curves of 694 human cell lines irradiated in exponentially growing phase *in vitro* were collected from the literature. Among them, 271 were derived from tumors, 423 were nontransformed fibroblasts and other normal cell strains from healthy people or people with some genetic disorders. Seventy-six different cell types are identified, and a specific radiosensitivity could be associated with each, using $\bar{D}$ and surviving fraction at 2 Gy. Technical factors such as culture medium, feeder cells, and scoring method were found to affect intrinsic radiosensitivity. In particular, the cell type is not a discriminating factor when cells are studied in agar. Results obtained with cells irradiated in agar must be used cautiously, depending on how the cells were prepared for the experiments. The use of feeder cells narrows the range of radiosensitivity of human cells. For cells irradiated as monolayer, it was possible to build a scale of radiosensitivity according to cell type, ranging, in terms of $\bar{D}$ from 0.6 Gy for the most sensitive cell lines to more than 4 Gy for the most resistant. Considering that, in most cases, we could estimate the variation of radiosensitivity within each cell type, our classification among cell types can be used by researchers to place their results in the context of the literature.

- 694 human cell lines (271 tumors from 24 tumors types, 423 normal tissue)
- Sensitivity scale according to cell type based on dose from 0.6 Gy for most sensitive to 4 Gy for most resistant

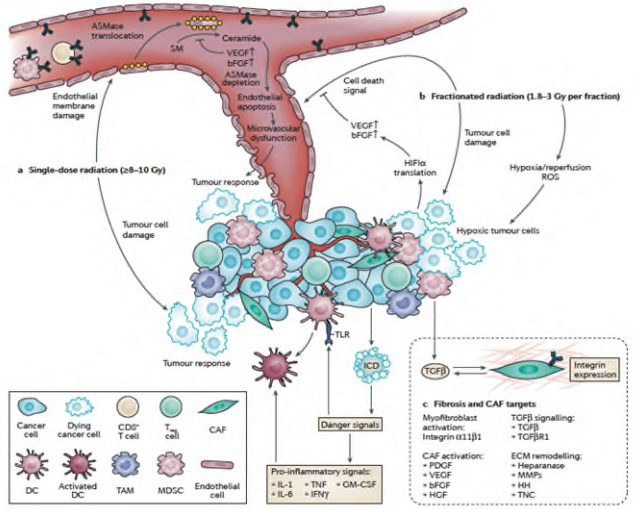
Table 2. (*Cont'd*)

Tumor cell lines	Fibroblastic and normal cell strains	*n*	$\bar{D}$ Mean (Gy)	$\bar{D}$ CV (%)	S2 Mean	S2 CV (%)
Stomac cancer		2	2.79	27	0.58	24
Glioblastoma		7	3.10	41	0.58	36
Bladder carcinoma		5	3.22	6	0.63	8
Ewing's sarcoma		1	3.27	—	0.65	—
	Kidney	1	3.29	—	0.67	—
Renal cell carcinoma		1	4.80	—	0.81	—

Cell types are ranked by increasing values of $\bar{D}$, *(fib) = fibroblast.



- Clonogenic survival assay of two RCC cell lines
- Small fraction cell kill at 0-6 Gy and exponential cell kill at doses > 6 Gy



- More effective cell kill
  - Endothelial cell apoptosis
  - Alternative tumor cell death
  - Pro-inflammatory signaling for adaptive immunity

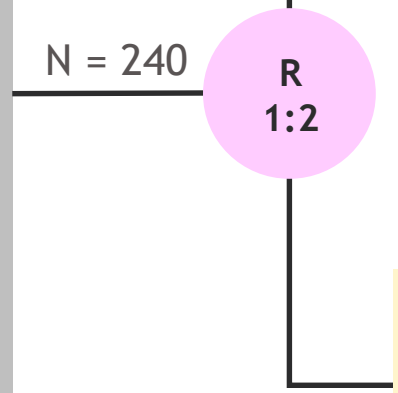
Deschavanne et al, IJROBP, 1996; Ning et al, Cancer, 1997; Siva et al, Nature Reviews Urology, 2017

On the Horizon: Targeting the Renal Primary

SAMURAI Randomized Phase 2

Key inclusion criteria:

- Metastatic RCC
- IMDC risk factors ≥ 1
- Primary lesion ≤ 80cm
- Amenable to treatment with SBRT to primary lesion



Standard immunotherapy-based regimen

(Allow for cytoreductive nephrectomy)

Standard immunotherapy-based regimen[a] + SBRT to primary (42 Gy/3)

(Allow for cytoreductive nephrectomy)

NRG ONCOLOGY™

PI: W. Hall, R. McKay

NOW ENROLLING!

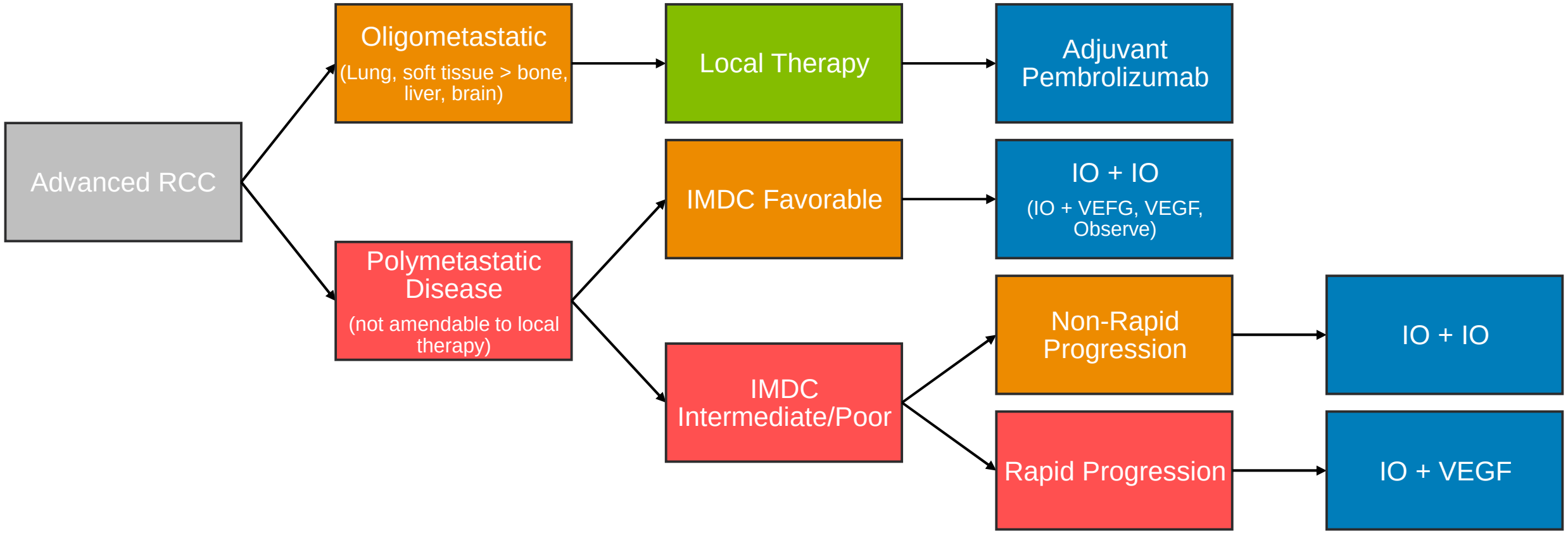
Stratification:

- Combination therapy (IO-VEGF vs. IO-IO)
- IMDC risk group (intermediate vs. poor)
- Histology (clear cell vs. non clear cell)

Primary endpoint: Radiographic Progression Free Survival

[a] Options (physician choice): e.g. Nivolumab + Ipilimumab, Pembrolizumab + Axitinib; Nivolumab + Cabozantinib, Pembrolizumab + Lenvatinib

Practical Approach for RCC Treatment – 2/2026



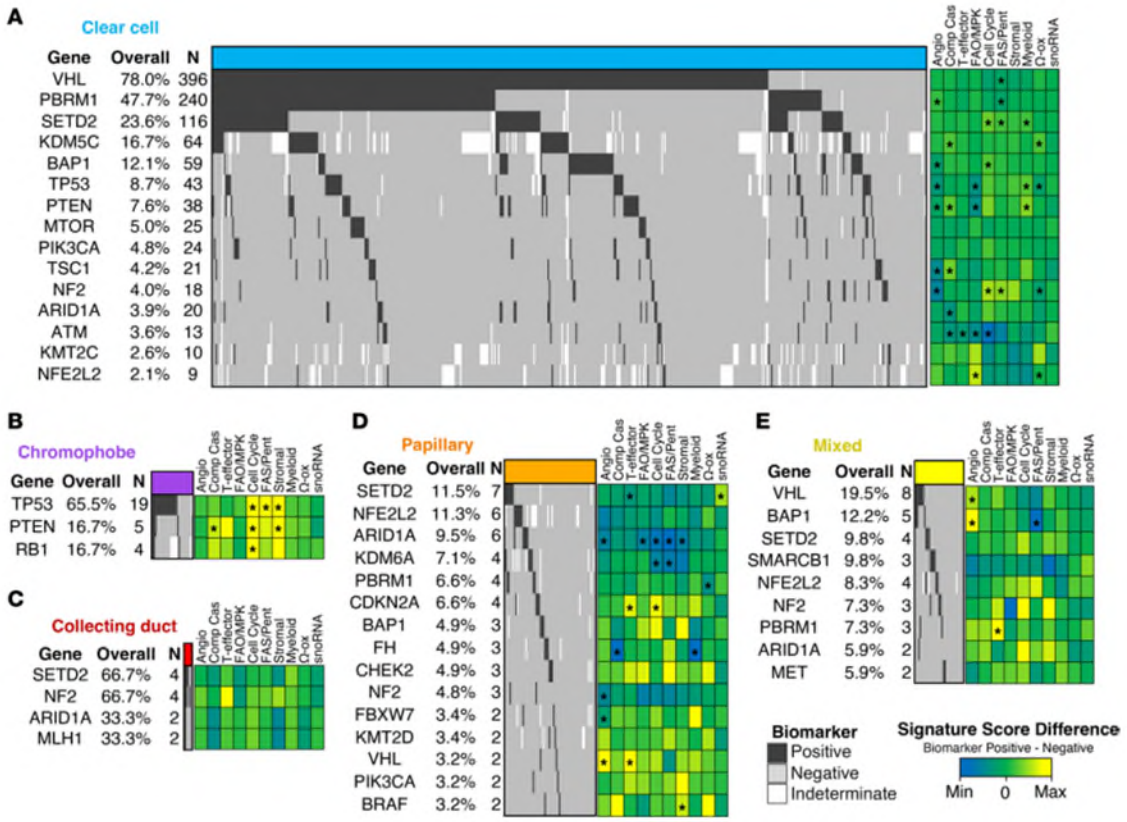
VHL Mutations Drives Pathogenesis in RCC

Identification of the von Hippel–Lindau Disease Tumor Suppressor Gene

Farida Latif, Kalman Tory, James Gnarra, Masahiro Yao, Fuh-Mei Duh, Mary Lou Orcutt, Thomas Stackhouse, Igor Kuzmin, William Modi, Laura Geil, Laura Schmidt, Fangwei Zhou, Hua Li, Ming Hui Wei, Fan Chen, Gladys Glenn, Peter Choyke, McClellan M. Walther, Yongkai Weng, Dah-Shuhn R. Duan, Michael Dean, Damjan Glavač, Frances M. Richards, Paul A. Crossey, Malcolm A. Ferguson-Smith, Denis Le Paslier, Ilya Chumakov, Daniel Cohen, A. Craig Chinault, Eamonn R. Maher,* W. Marston Linehan,* Berton Zbar,* Michael I. Lerman*

A gene discovered by positional cloning has been identified as the von Hippel–Lindau (VHL) disease tumor suppressor gene. A restriction fragment encompassing the gene showed rearrangements in 28 of 221 VHL kindreds. Eighteen of these rearrangements were due to deletions in the candidate gene, including three large nonoverlapping deletions. Intragenic mutations were detected in cell lines derived from VHL patients and from sporadic renal cell carcinomas. The VHL gene is evolutionarily conserved and encodes two widely expressed transcripts of approximately 6 and 6.5 kilobases. The partial sequence of the inferred gene product shows no homology to other proteins, except for an acidic repeat domain found in the procyclic surface membrane glycoprotein of *Trypanosoma brucei*.

In 1993, the VHL tumor suppressor gene was identified following positional cloning studies in VHL families

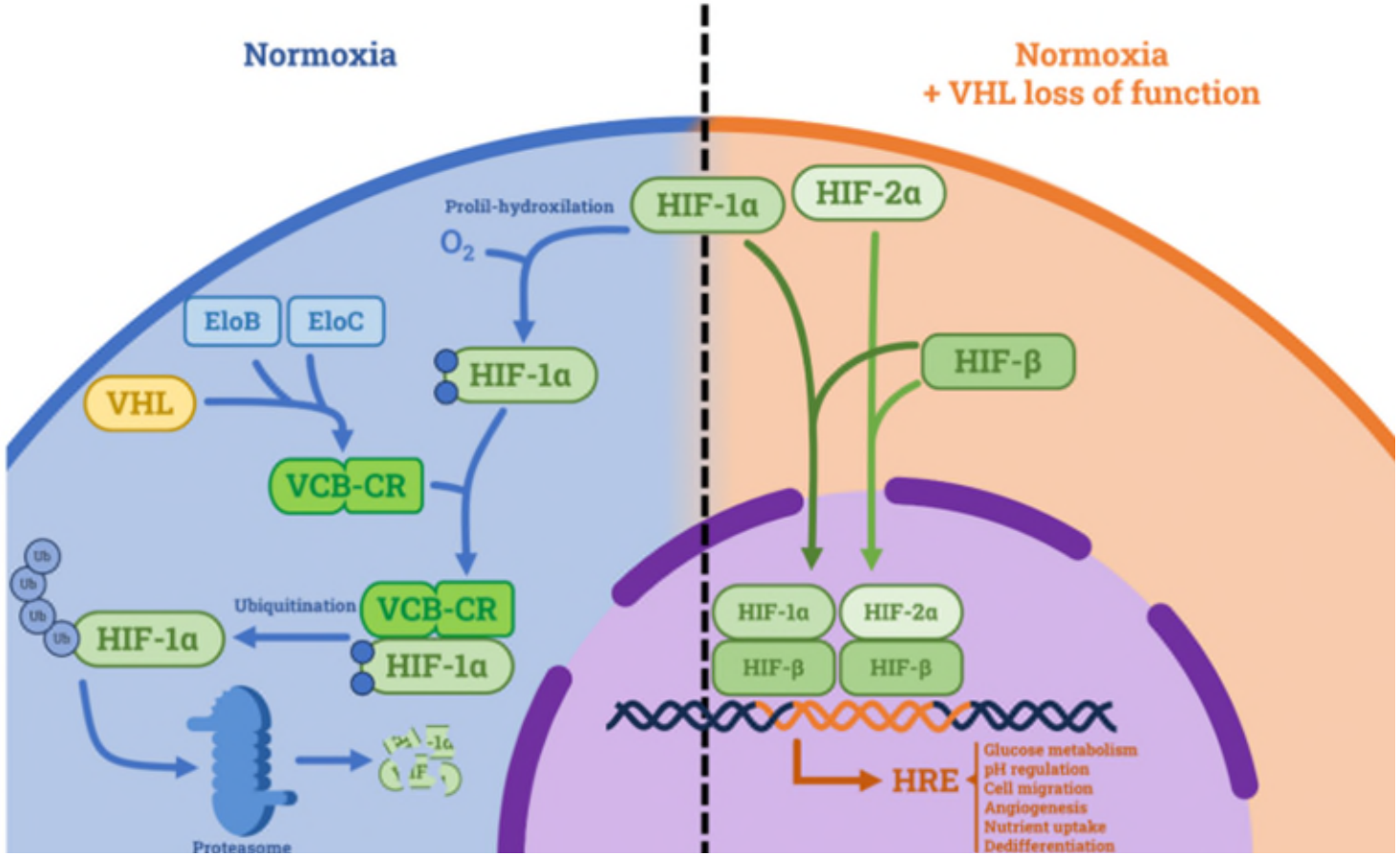


78% (n=396/508) of clear cell RCC with VHL mutations

VHL=Von Hippel Lindau; RCC=Renal cell carcinoma.

Latif et al, Science, 1993; Barata et al, JCI, 2024

HIF-VHL Pathway in RCC Pathogenesis



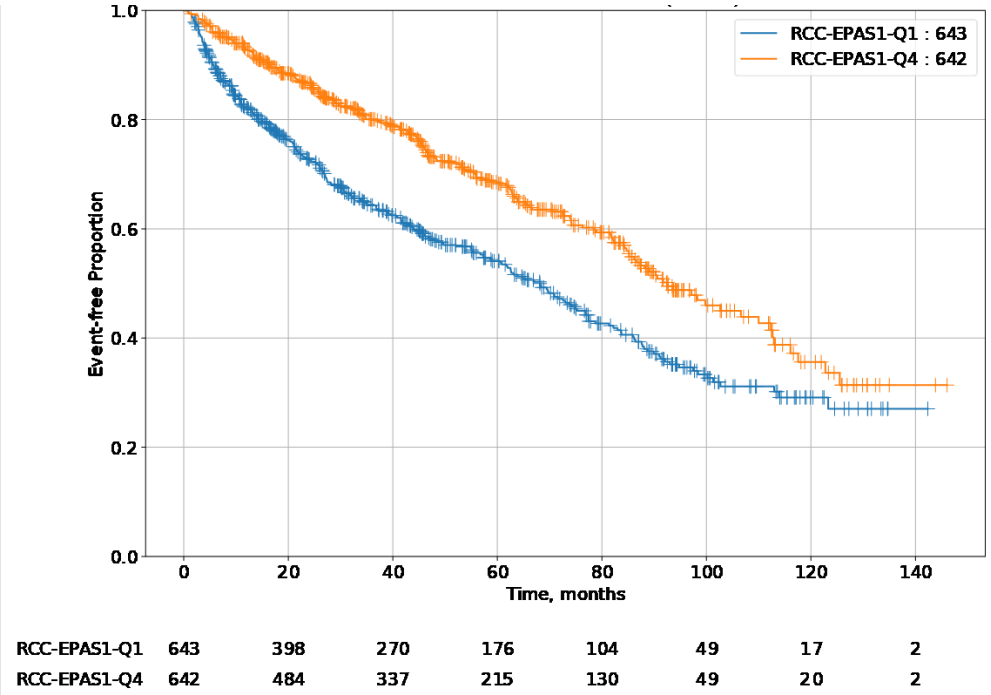
HIF=Hypoxia inducible factor; VHL=Von Hippel Lindau; RCC=Renal cell carcinoma.

Pezzicoli et al, Current Oncology, 2023

Outcomes by HIF-2α RNA Expression

Abstract 4543
Yu-Wei Chen
HIF family transcription factor expression in a cohort of 4362 patients with RCC

DNA/RNA Expression of 4362 RCC Patients



Overall Survival
92.6 vs. 68.1 months HIF-2α high vs. low quartile
HR 0.61 (95% CI 0.51-0.73)

	HIF-2α (% prevalence)		
	Low (Q1)	High (Q4)	q-value
BAP1	13.07	6.91	0.0004
KDM5C	4.33	11	<0.0001
KDM6A	2.64	0.16	0.0003
MTOR	1.46	4.31	0.0038
NF2	10.05	1.59	<0.0001
PBRM1	17.86	45.45	<0.0001
PIK3CA	3.4	3.03	0.733
PTEN	6.05	9.35	0.0369
SETD2	18.37	22.62	0.0784
SMARCB1	4.05	1.43	0.0059
TP53	14.22	9.11	0.0067
TSC1	4.54	3.52	0.3925
TSC2	0.81	1.12	0.6058
VHL	30.47	75.91	<0.0001

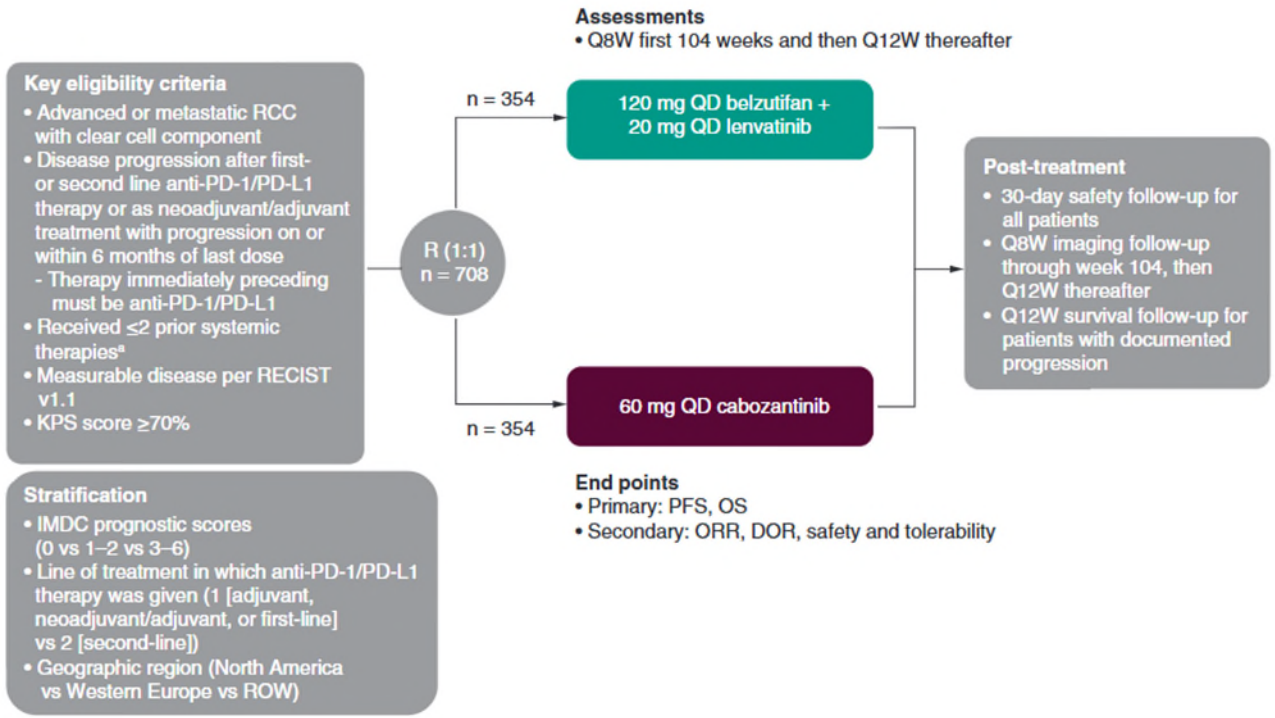
Differential DNA alterations in tumors with high HIF-2α expression

HIF=Hypoxia inducible factor; RCC=Renal cell carcinoma; HR=Hazard ratio; CI=Confidence interval.

HIF2α Inhibitor Trials in Refractory RCC

	LITESPARK-005	ARC-20	ARC-20	ARC-20	LITESPARK-003	Keymaker-U03	ARC-20
Treatment	Belzutifan vs. Everolimus	Casdatifan 50 mg BID	Casdatifan 50 mg daily	Casdatifan 100 mg daily	Belzutifan 120 mg daily + Cabozantinib 60 mg daily	Belzutifan 120 mg daily + Lenvatinib 20 mg daily	Casdatifan 100 mg daily + Cabozantinib 60 mg daily
Sample Size	N=746	N=32	N=28	N=27	N=52	N=63	N=24
ORR (%)	23%	25%	29%	33%	31%	47%	46%
PFS, median (months)	5.6	NR	NR	NR	13.8	12.5	NR
HR (95% CI)	0.74 (0.63-0.88)	-	-	-	-	-	-
OS, median, months	21.4	-	-	-	26.7	-	-
HR (95% CI)	0.88 (0.73-1.07)	-	-	-	-	-	-

Litespark-011 – Belzutifan + Lenvatinib in Later Line



Media > News releases > News release

Merck and Eisai Announce WELIREG® (belzutifan) Plus LENVIMA® (lenvatinib) Met Primary Endpoint of Progression-Free Survival (PFS) in Certain Previously Treated Patients With Advanced Renal Cell Carcinoma

Save

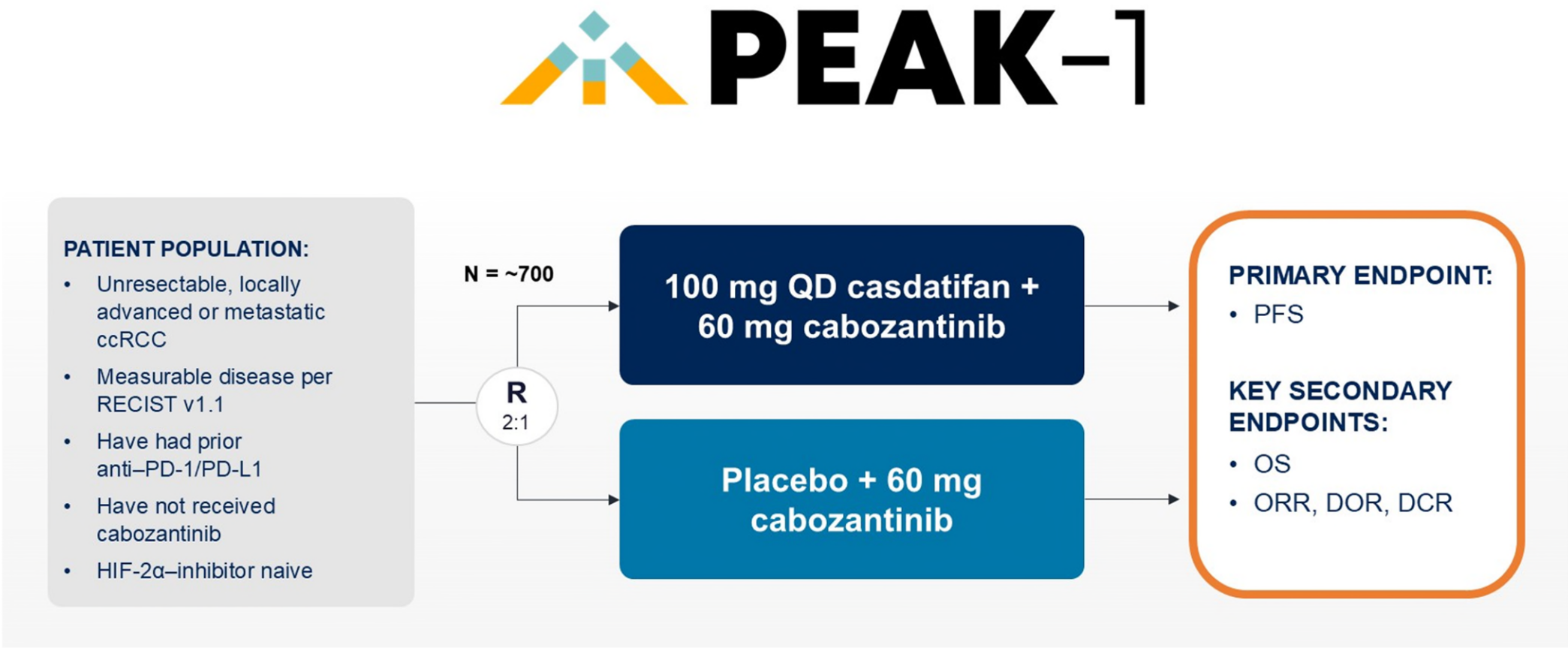
October 28, 2025 6:30 am EDT

First treatment regimen to demonstrate a statistically significant improvement in PFS for patients whose disease progressed following anti-PD-1/L1 therapy compared with cabozantinib in a Phase 3 study

LITESPARK-011 marks the first positive Phase 3 study of a HIF-2 alpha inhibitor in combination with a multi-targeted VEGF tyrosine kinase inhibitor

RAHWAY, N.J. & NUTLEY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, and Eisai today announced that the Phase 3 LITESPARK-011 trial evaluating the dual oral regimen of WELIREG® (belzutifan), Merck's first-in-class oral hypoxia-inducible factor-2 alpha (HIF-2α) inhibitor, plus LENVIMA® (lenvatinib), an orally available multiple receptor tyrosine kinase inhibitor (TKI) discovered by Eisai, met one of its primary endpoints of progression-free survival (PFS) for the treatment of patients with advanced renal cell carcinoma (RCC) whose disease progressed on or after treatment with anti-PD-1/L1 therapy.

PEAK-1 – Casdatifan + Cabozantinib



Advanced Urologic Cancer Consensus Conference (AUC3)

Received: 15 September 2025 | Revised: 7 October 2025 | Accepted: 22 October 2025

DOI: 10.3322/caac.70052

REVIEW ARTICLE

Advanced Urologic Cancer Consensus Conference (AUC3) 2025: Expert consensus on the management of renal cell and urinary tract cancers

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Abstract

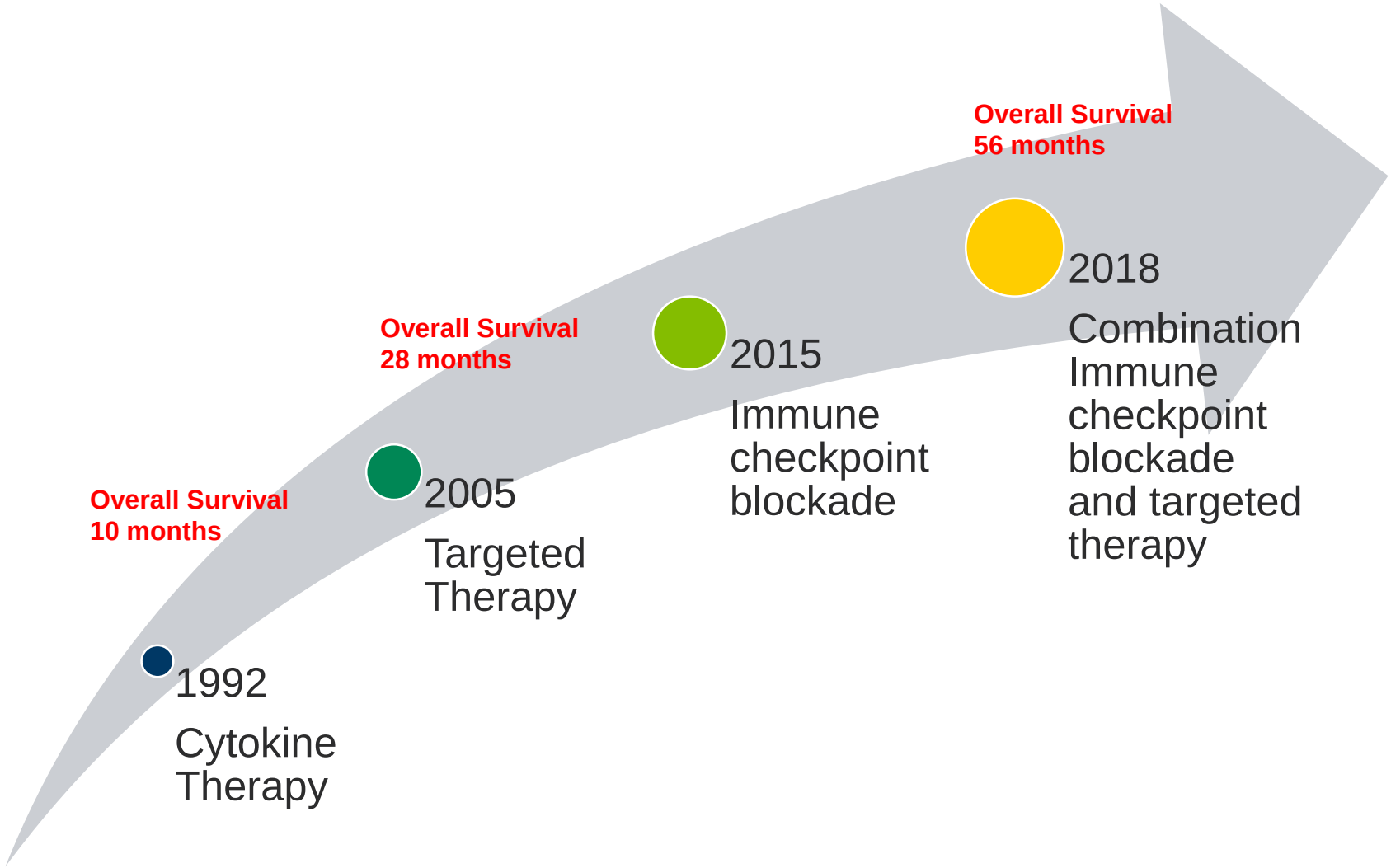
The therapeutic landscape for renal cell carcinoma (RCC) and urinary tract cancer (UTC) has transformed dramatically, creating complexity in treatment selection and sequencing. The 2025 Advanced Urologic Cancer Consensus Conference was convened to establish evidence-based expert consensus recommendations for

Renal Cell Carcinoma Consensus

Clinical Scenario	Strong Consensus	Agreement %
ADJUVANT & LOCALLY ADVANCED RCC		
pT3bN1 with sarcomatoid features	Adjuvant pembrolizumab	97.8%
pT3a grade 3-4	Adjuvant pembrolizumab	95.5%
pT3b grade 3-4	Adjuvant pembrolizumab	95.3%
pT4 any grade	Adjuvant pembrolizumab	95.6%
pTxN1 any grade	Adjuvant pembrolizumab	90.7%
METASTATIC CLEAR CELL RCC		
Metastatic sarcomatoid ccRCC	Nivolumab + ipilimumab preferred	93.2%
ICI + TKI regimen dosing	Start VEGF-TKI at recommended dose	100.0%
TREATMENT SEQUENCING		
Fourth-line therapy selection	Use TKI not previously received	100.0%
Fifth-line therapy in fit patients	Offer treatment versus best supportive care	95.1%
NON-CLEAR CELL RCC		
Metastatic renal medullary carcinoma	Platinum-based chemotherapy	90.5%

Clinical Scenario	Consensus	Agreement %
ADJUVANT & LOCALLY ADVANCED RCC		
pT2 grade 4	Recommend adjuvant pembrolizumab	80.0%
pTxNxM1 resected to NED within 1 year	Recommend adjuvant pembrolizumab	81.8%
cT3N0M0 renal mass biopsy	Rarely perform biopsy before surgery	75.6%
Pre-adjuvant therapy workup	Always perform restaging	82.2%
Nephrectomy causing anephric state	Usually avoid	82.2%
METASTATIC CLEAR CELL RCC		
Aggressive biology management	Avoid surveillance/local therapy alone	81.4%
Rapidly progressive metastatic ccRCC	ICI + VEGF-TKI	81.0%
ICI re-challenge after adjuvant pembrolizumab	Generally acceptable	92.9%
Relapse 0-3 months after starting adjuvant	Do NOT re-challenge	85.4%
Relapse 12-24 months post-completion	Re-challenge appropriate	92.7%
Relapse >24 months post-completion	Re-challenge appropriate	95.1%
TREATMENT SEQUENCING		
Second-line after axitinib + pembrolizumab	Cabozantinib	85.0%
After ipilimumab + nivolumab progression	TKI monotherapy	90.0%
Solitary progression on ipilimumab + nivolumab	Local therapy + continue nivolumab	85.7%
Early progression on cabozantinib + nivolumab	Switch to lenvatinib + everolimus	75.6%
Third-line (post lenvatinib + pembrolizumab → cabozantinib)	Belzutifan	81.0%
Belzutifan-induced anemia	Use ESA	84.6%
Belzutifan-induced hypoxia	Hold drug, dose reduce when O2 >92%	92.7%
NON-CLEAR CELL RCC		
Papillary RCC (high-risk)	Do NOT recommend adjuvant pembrolizumab	83.3%
Non-clear cell RCC workup	Obtain somatic genomic profiling	88.4%
Terminology for non-clear cell tumors	Use exact histology terms	90.7%
Metastatic non-clear cell RCC workup	Obtain somatic genomic profiling	88.1%
Approach for non-clear cell RCC	Differ by exact histology	90.7%
	-based chemotherapy	82.9%

Decades of Progress



Conclusions

- Significant advances in our understanding of cancer and RCC tumor biology has resulted in improved therapeutic options for patients in the clinical
- Survival has dramatically improved for patients with RCC over the past decade and approaches 5 years in the modern era
- Frontline treatment for patients with advanced RCC includes immunotherapy combinations and choice of therapy is dependent on goals of care and clinical characteristics
- Subsequent line treatment options are evolving and at the present time include VEGF monotherapy as the backbone of systemic therapy
- Additional ongoing clinical trials will further inform the treatment landscape for patients with metastatic and advanced RCC

UC San Diego Health

Questions?