Dana-Farber Cancer Institute

BRIGHAM HEALTH
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HARVARD MEDICAL SCHOOL

@DrChoueiri

Avoiding Pitfalls in Designing the Next Generation of Clinical Trials in Renal Cell Carcinoma

MLS CLEVELAND August 19th, 2023

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Jerome and Nancy Kohlberg Professor of Medicine
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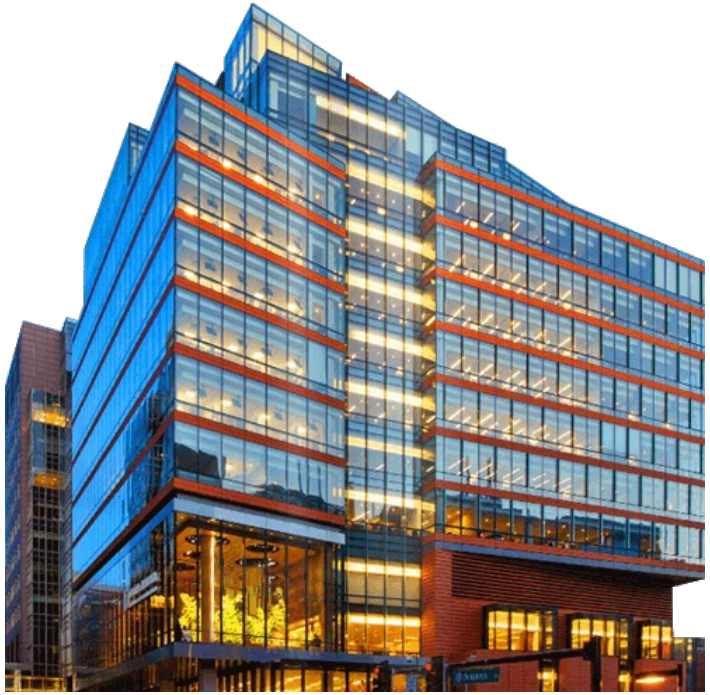


Some Facts about today's RCC landscape:

What worked, did not work, and next steps in the context of:

- 1L metastatic ccRCC
- The de-facto post PD-1 setting
- The non-clear cell RCC setting
- The adjuvant setting
- Less focus on "novel targets and agents" and new clinical trials endpoints in RCC

Some Facts about today's RCC landscape: What worked and what did not work

- 1L metastatic ccRCC
- The de-facto post PD-1 setting
- The non-clear cell RCC setting
- The adjuvant setting

1L metastatic ccRCC: what worked

- 1L therapies consist in concomitant doublets:
  - **PD-1+VEGF TKI**
  - **PD-1+CTLA-4**
  - No need to review what everyone knows in this room, circa all Educational/CME conferences since 2018….

1L metastatic ccRCC: what did not work

- 1L therapies with sequential doublets:
  - Sequential approaches of A followed by A+B with the *hope* of decreasing toxicity and maintaining (or even optimizing responses):

Example: PD-1→ PD1+CTLA-4

METASTATIC RCC TRIALS FOR SEQUENCING AND OPTIMIZATION (SLIDE FROM 2016, STILL RELEVANT)

Sequencing

NivoSwitch
- Nivolumab or continuation of therapy on TKI post 3 months

NCT03035630
- Sunitinib followed by avelumab or avelumab followed by sunitinib

Checkmate 800
- Study of multiple administration regimens for nivolumab + ipilimumab

Treatment Optimization

HCRN- GU16-260
- 1L therapy with nivolumab and salvage nivolumab + ipilimumab in advanced or metastatic RCC

OMNIVORE (DFCI)
- Response-based approach to treatment with nivolumab in advanced or metastatic RCC

TITAN RCC
- Tailored ImmunoTherapy Approach With Nivolumab in Subjects With Metastatic or Advanced Renal Cell Carcinoma

SAKK 07/17:
- Nivolumab in Combination With Ipilimumab in Patients With Metastatic Renal Cell Carcinoma

CASE 5816:
- Intermittent Nivolumab in Metastatic Renal Cell Carcinoma Patients

Observations and Lessons learned

- Hard to accrue
- Academic-led
- Smaller size
- Some not even reported (yet?)
- Some did not survive the rapid change in SOC

Treatment Optimization

OMNIVORE[1]

Key inclusion criteria
- mRCC, any histology
- Untreated or previously treated
- No prior CPI
- Measurable disease by RECIST v1.1
- ECOG PS 0-2

Nivolumab induction

Tumor assessments wk 8, 16, 20

- Confirmed CR/PR within 6 mo → **Arm A:** Stop treatment
- Confirmed SD → **Arm B:** Add **ipilimumab**
- PD → **Arm B:** Add **ipilimumab**

HCRN GU16-260[2]

Key inclusion criteria
- mRCC, any histology
- Treatment naïve
- Measurable disease by RECIST v1.1
- ECOG PS 0-2

Part A

Nivolumab induction

- PR or CR → **Part B:** Continue **nivolumab** for ≤96 total wk
- PD or best response SD at 48 wk → **Nivolumab + ipilimumab** every 3 wk x 4 then **nivolumab** maintenance ≤48 wk

Conclusions

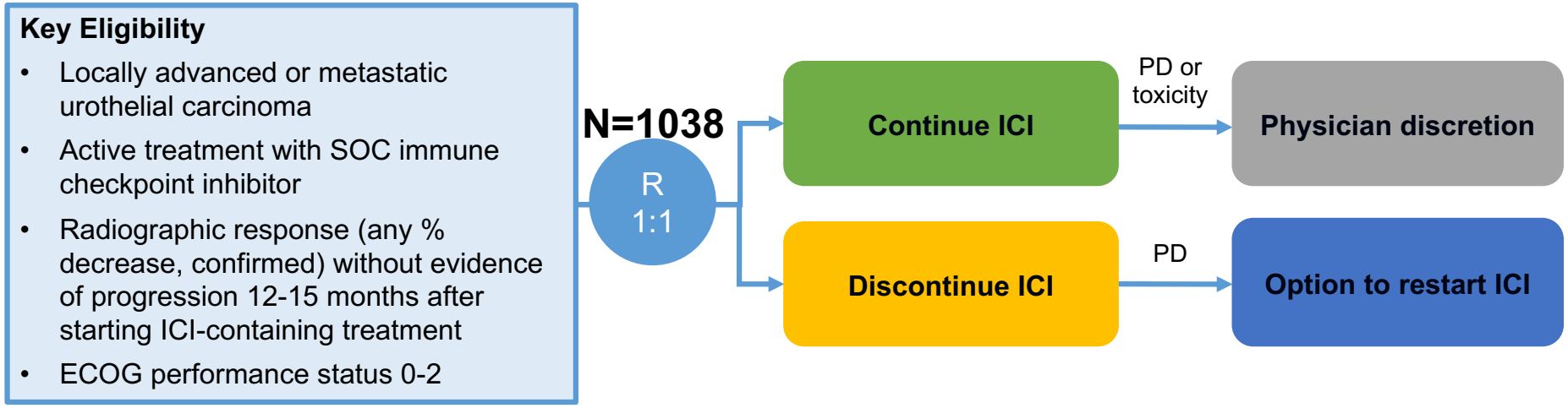
- Upfront combination of nivolumab + ipilimumab preferred over nivolumab followed by nivolumab + ipilimumab:
  - **-Low CR rate (<5%) with sequential approach**
  - **-Significant attrition rate (30-50%)**
- Biologic predictors of responses needed

1. McKay RR et al. JCO 2020. Abstract 5005. 2. Atkins MB et al. ASCO 2020. Abstract 5006.

What about Duration of Immunotherapy in mRCC?

A Randomized Phase 3 Non-inferiority Trial (but in met. Bladder Cancer)

ALLIANCE Trial



15 NOV 2022: STOPPED BY DSMC FOR POOR ACCRUAL

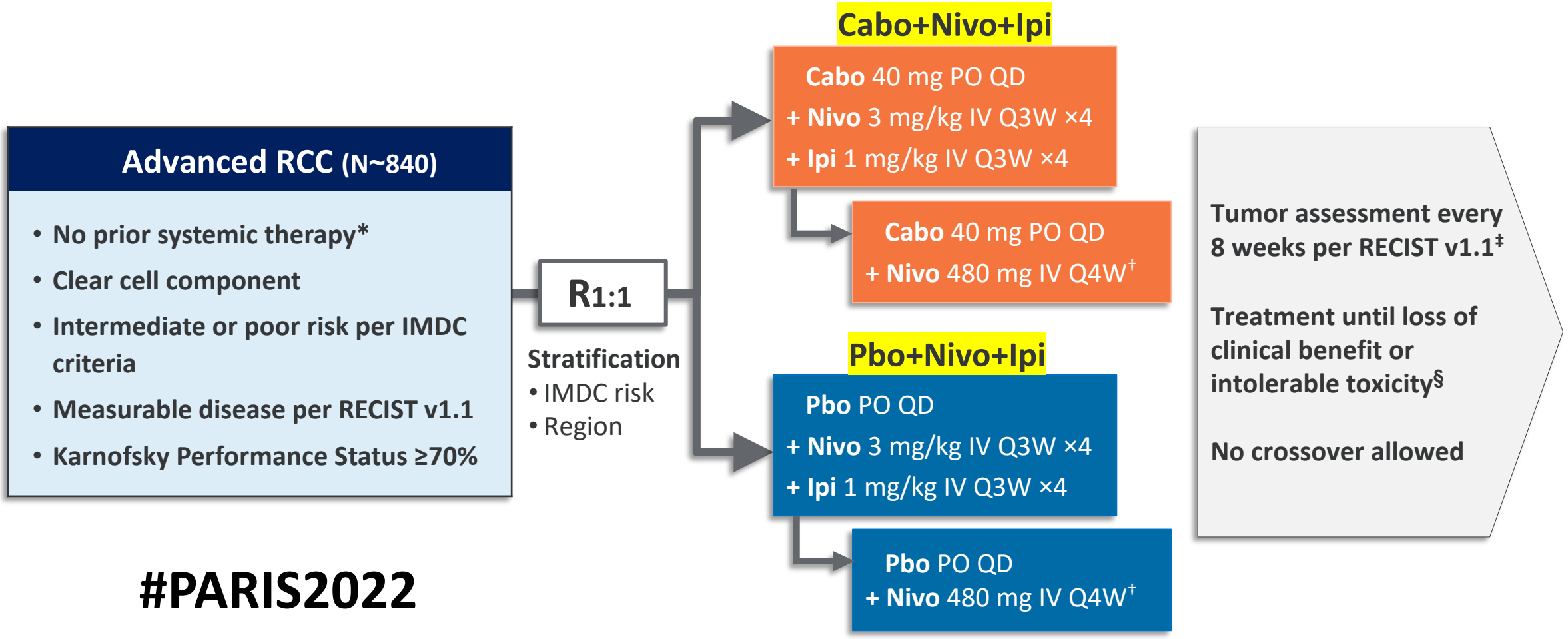
The study enrolled 3 patients in just-shy-of-2 years

Study Chair: Xiao Wei
Study Co-Chair: Toni Choueiri

1L metastatic ccRCC: current realities and “ongoing designs”

- ADDITIVE (COSMIC-313): 3 vs. 2 (SOC).
- ADAPTIVE (PDIGREE): 2 (SOC) then decide.
- SEQUENTIAL (TIDE): still ongoing, but in highly-selected patients.
- ORGAN-BASED (RADICAL): Bone metastases in RCC as an unmet medical need

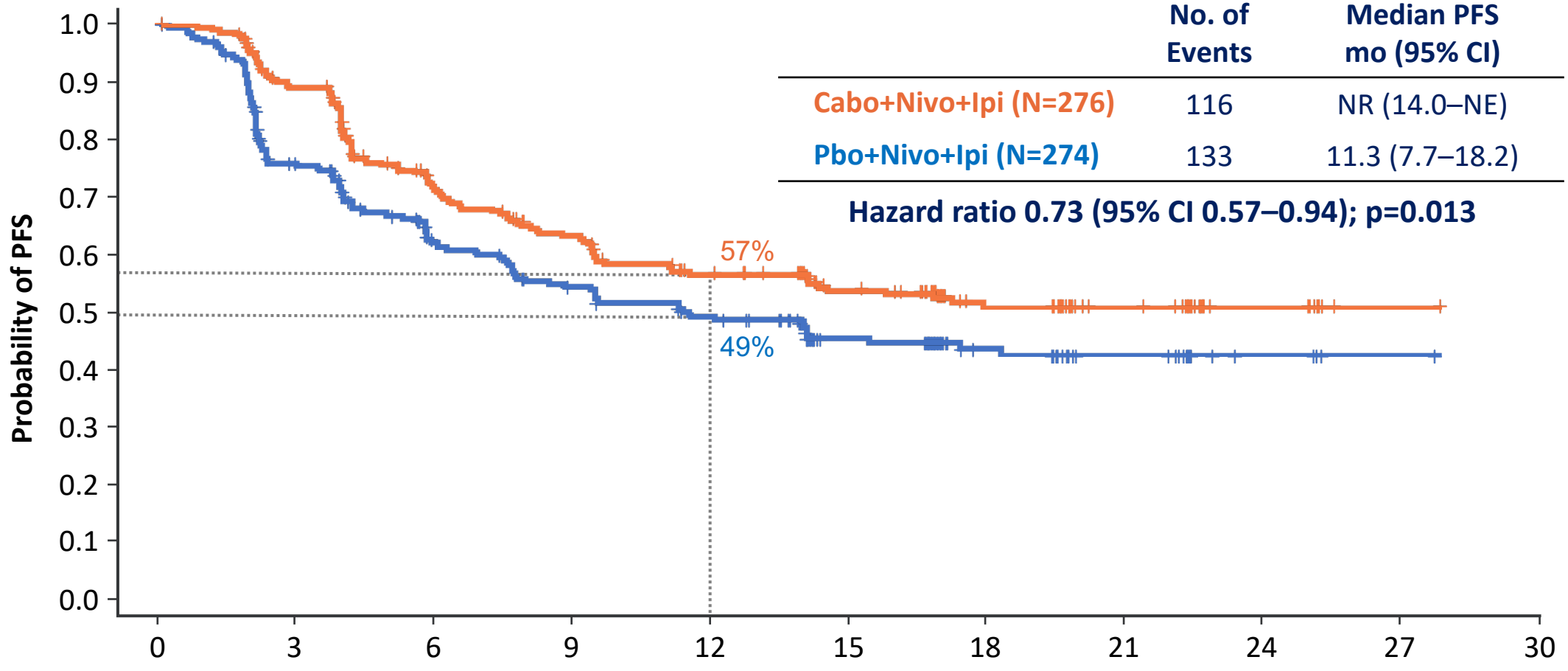
ADDITIVE DESIGN: COSMIC-313 Study



#PARIS2022

*One prior systemic adjuvant therapy allowed for completely resected RCC and if recurrence occurred ≥6 months after the last dose of adjuvant therapy; adjuvant PD-1 or PD-L1 inhibitor in combination with a CTLA-4 inhibitor not permitted. †Nivolumab given for a maximum of 2 years. ‡Tumor assessment (RECIST v1.1) at week 10, then every 8 weeks through week 50, then every 12 weeks thereafter. §Discontinuation of one agent did not mandate discontinuation of all agents.

Progression-Free Survival: Final Analysis (PITT Population)



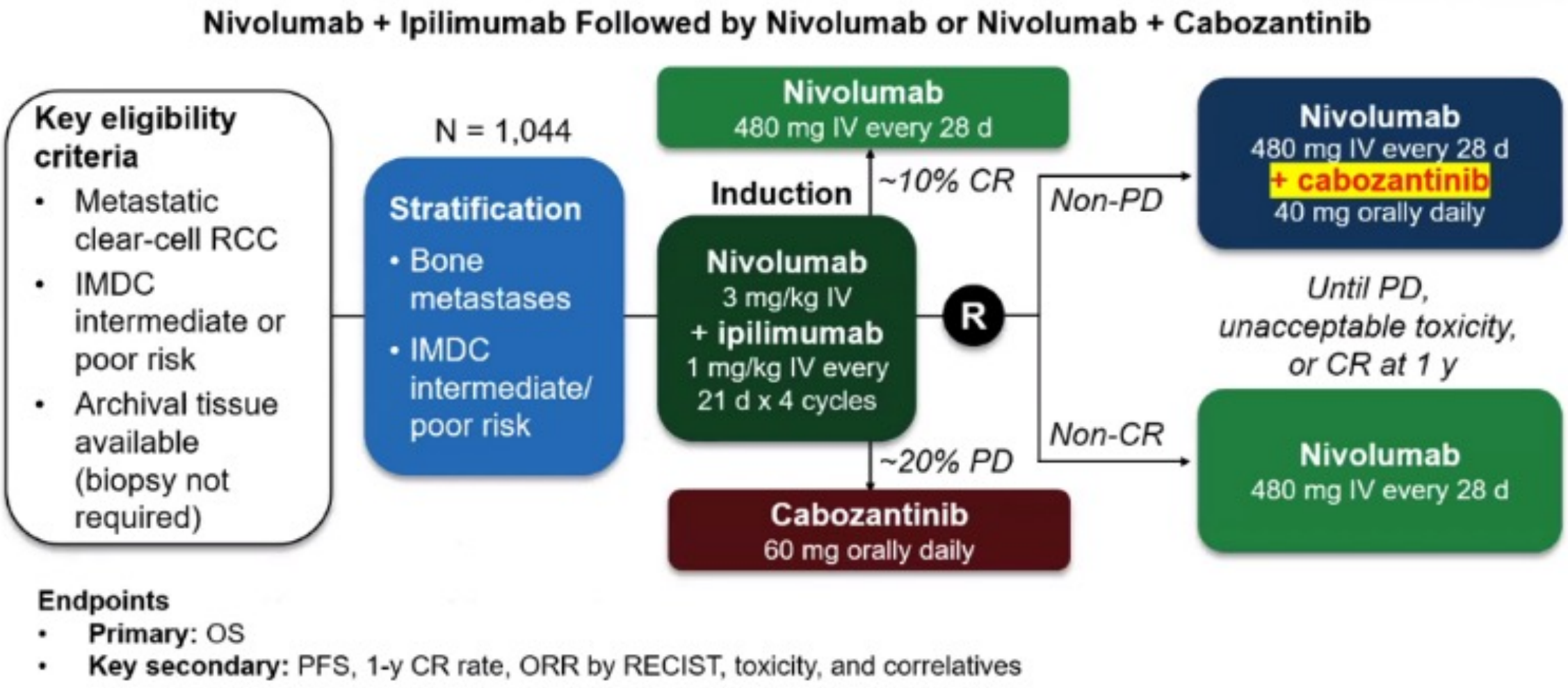
	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=276)	116	NR (14.0–NE)
Pbo+Nivo+Ipi (N=274)	133	11.3 (7.7–18.2)

Hazard ratio 0.73 (95% CI 0.57–0.94); p=0.013

Number at Risk											
Cabo+Nivo+Ipi	276	234	170	145	119	97	56	33	10	1	0
Pbo+Nivo+Ipi	274	185	136	115	98	69	37	19	5	1	0

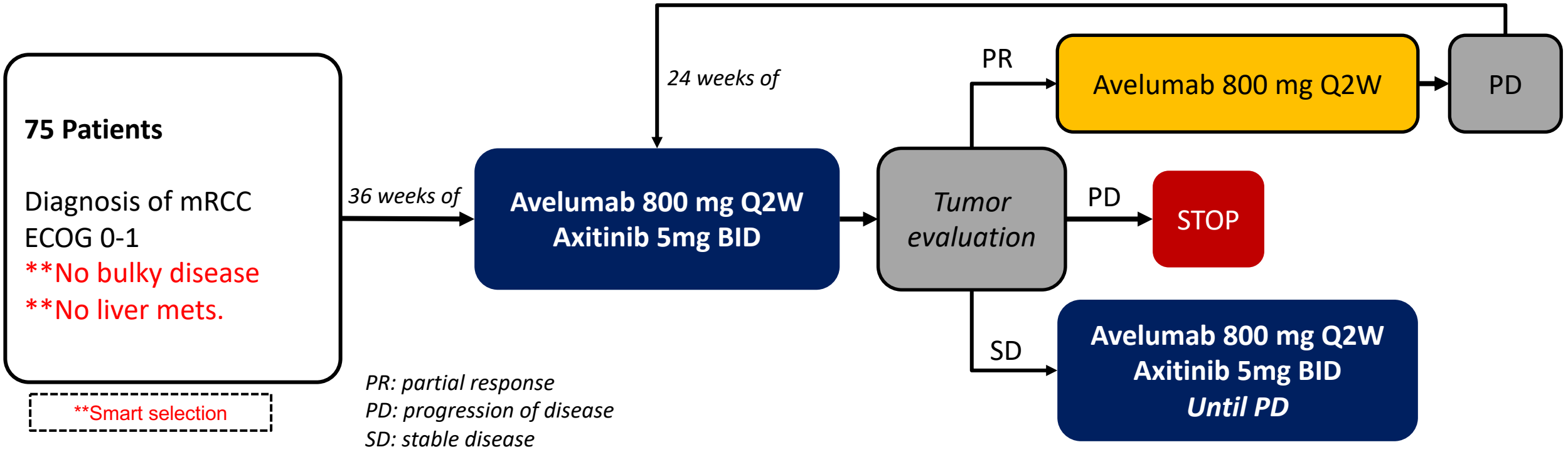
Choueiri et al, ESMO 22 and NEJM 2023

Adaptive Design: Phase III PDIGREE Trial (Alliance)



PI: Zhang and Choueiri (ALLIANCE)

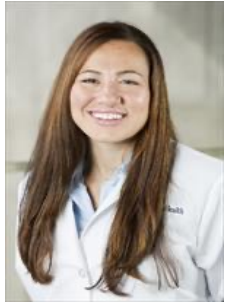
SEQUENTIAL DESIGN: PD-L1 inhibitor→ TKI (TIDE)



ClinicalTrials.gov Identifier: NCT04698213

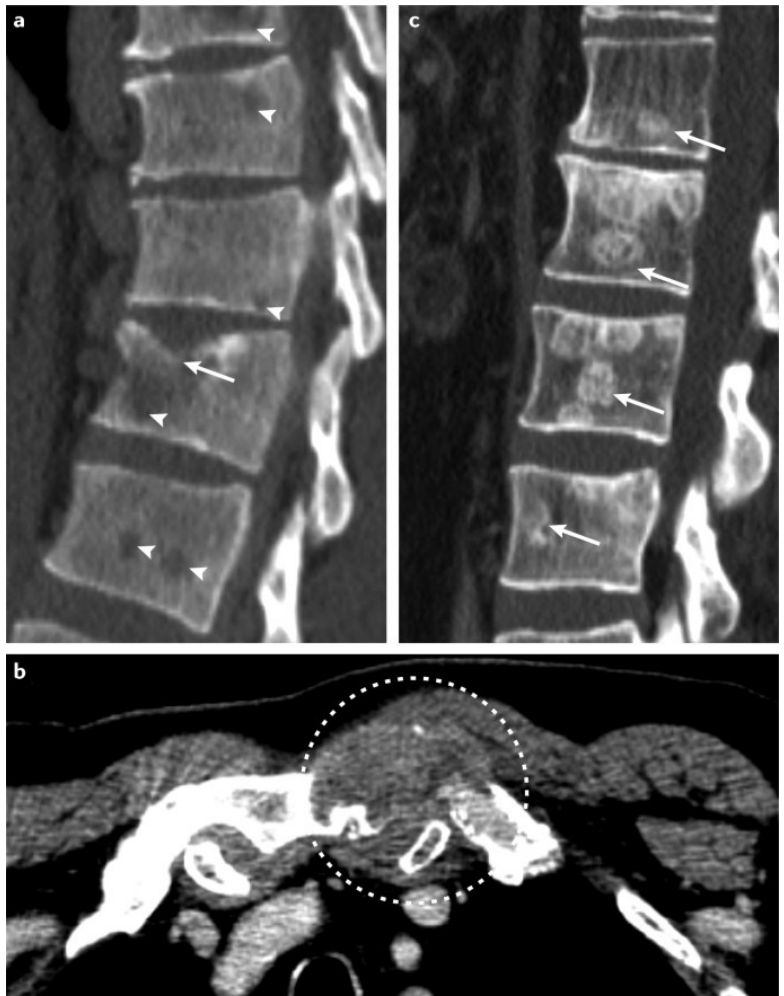
Iacovelli et al, ASCO GU 2020 TPS762

Do we do Site/Organ-Specific Clinical trials?



R. McKay

The Case for BONE METS (unmet medical need)



- Bone mets have an independent adverse prognosis in mRCC (McKay and Choueiri):

1. IMDC data (Eur. Urol. 2014)
2. Clinical Trials database: confirmed and Bisphosphonates did not affect survival or SRE prevention and was associated with increased toxicity. (Eur. Urol 2014)

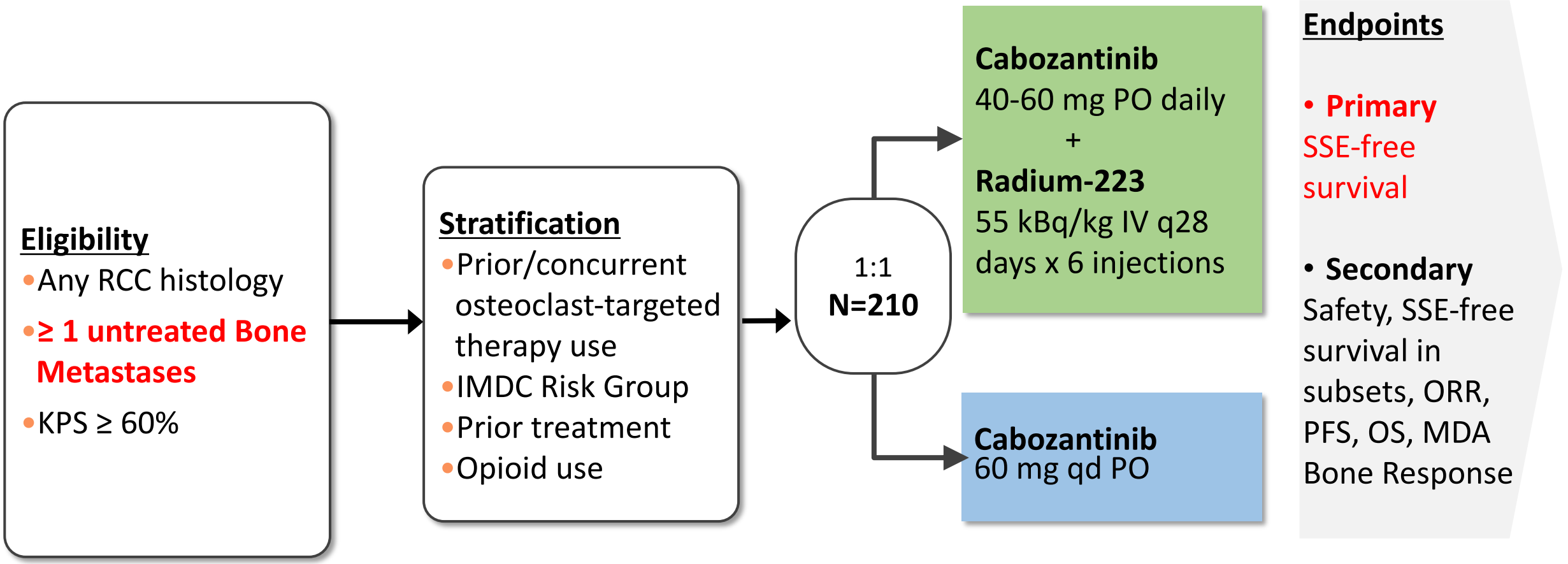
Clinical Trials: Targeted Therapy

Clinical Cancer Research

Radium-223 Dichloride in Combination with Vascular Endothelial Growth Factor–Targeting Therapy in Advanced Renal Cell Carcinoma with Bone Metastases

Rana R. McKay[1,2], Dominick Bossé[2], Kathryn P. Gray[3], M. Dror Michaelson[4], Katherine Krajewski[5], Heather A. Jacene[5], Meghara Walsh[3], Joaquim Bellmunt[2], Mark Pomerantz[2,5], Lauren C. Harshman[2,5], and Toni K. Choueiri[2,5]

Organ-Based: RADICAL/A031801 (PI: McKay/Choueiri)



N=210 (non-clear cell cap at 20%)
90% power, α=0.025 (one-sided)
Detect improvement of 6-month SSE-FS from 65% to 78%

Imaging, QOL, biomarker assessment every 8 weeks

NCT04071223

Some Facts about today's RCC landscape:
What worked and what did not work

- 1L metastatic ccRCC
- The de-facto post PD-1 setting
- The non-clear cell RCC setting
- The adjuvant setting

The de-facto post PD-1 setting

Many questions and answers, but to me most important:

- Can we use PD1/L1 inhibitors post progression on PD1/L1?

  ✓ FRACTION-RCC[1] (Nivo+Ipi) and PD-1+TKI phase II trials (e.g. Len+Pembro[2]) are single agent CTLA-4 and Lenvatinib activity respectively, until proven otherwise!

1. Choueiri et al, JITC 2022
2. Lee at al, Lancet Oncol 2021

Phase III CONTACT-03 study

Key eligibility criteria

- Advanced/metastatic clear cell or non–clear cell[a] RCC with or without a sarcomatoid component
- Radiographic progression on or after prior ICI treatment
  - ICI as adjuvant, 1L or 2L (single agent or in combination with another permitted agent)
  - ICI in the immediately preceding line of therapy

R
1:1

N=522

Atezolizumab 1200 mg IV q3w + Cabozantinib 60 mg daily PO

Cabozantinib 60 mg daily PO

Stratification factors

- **IMDC risk group**
  0 vs 1-2 vs ≥3
- **Histology**
  Dominant clear cell without sarcomatoid vs dominant non-clear cell without sarcomatoid vs any sarcomatoid[b]
- **Most recent line of ICI**
  Adjuvant vs 1L vs 2L

Primary endpoints

- Independent centrally-assessed PFS[c]
- OS

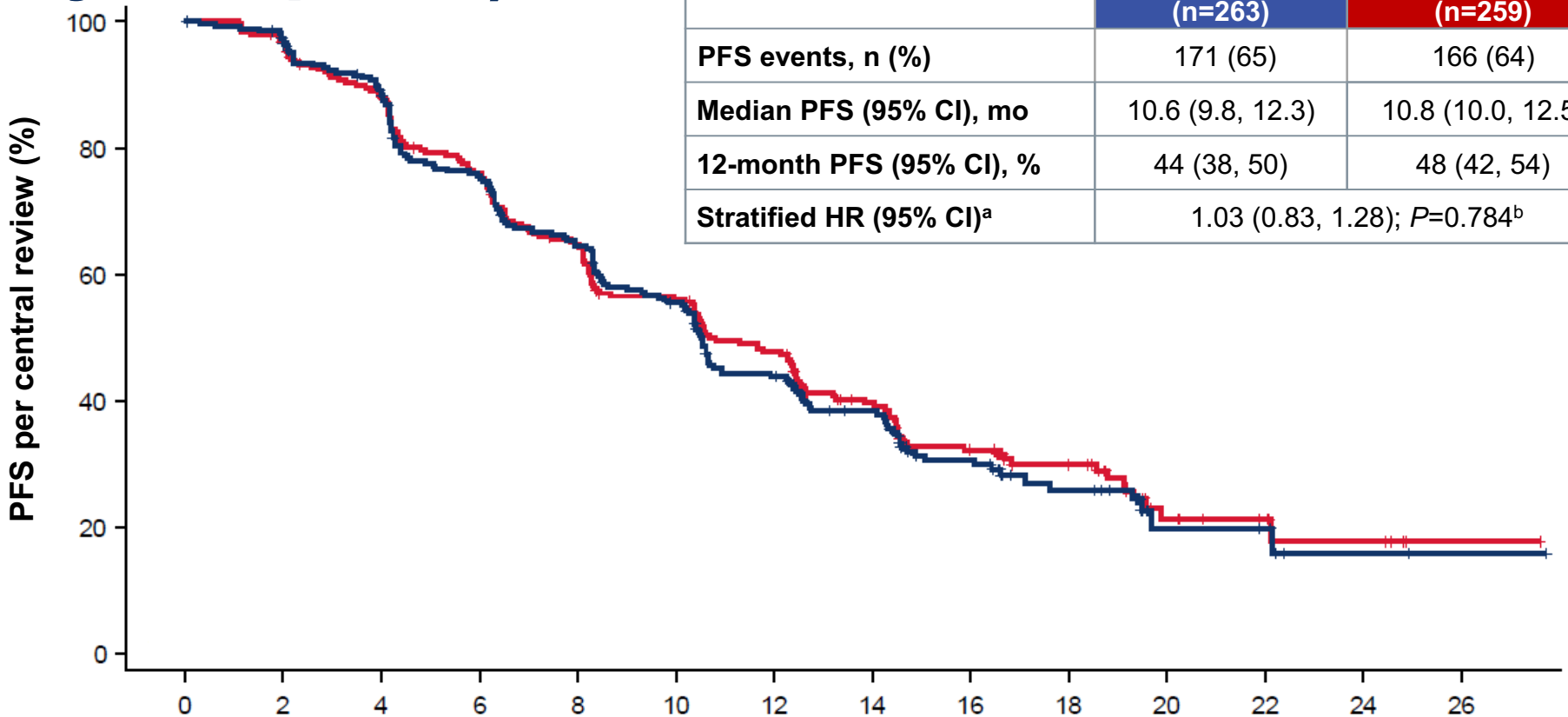
Key secondary endpoints

- Investigator-assessed PFS[c]
- ORR (per central review and per investigator)[c]
- Duration of response (per central review and per investigator)[c]
- Safety

ClinicalTrials.gov ID, NCT04338269. IMDC, International Metastatic RCC Database Consortium. Patients were enrolled between July 28, 2020 and December 27, 2021.
[a] Papillary, chromophobe or unclassified (chromophobe requires sarcomatoid differentiation). [b] Clear cell or non-clear cell. [c] Assessed according to RECIST 1.1.

Primary analysis of centrally reviewed PFS (primary endpoint)

	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	171 (65)	166 (64)
Median PFS (95% CI), mo	10.6 (9.8, 12.3)	10.8 (10.0, 12.5)
12-month PFS (95% CI), %	44 (38, 50)	48 (42, 54)
Stratified HR (95% CI)[a]	1.03 (0.83, 1.28); *P*=0.784[b]	

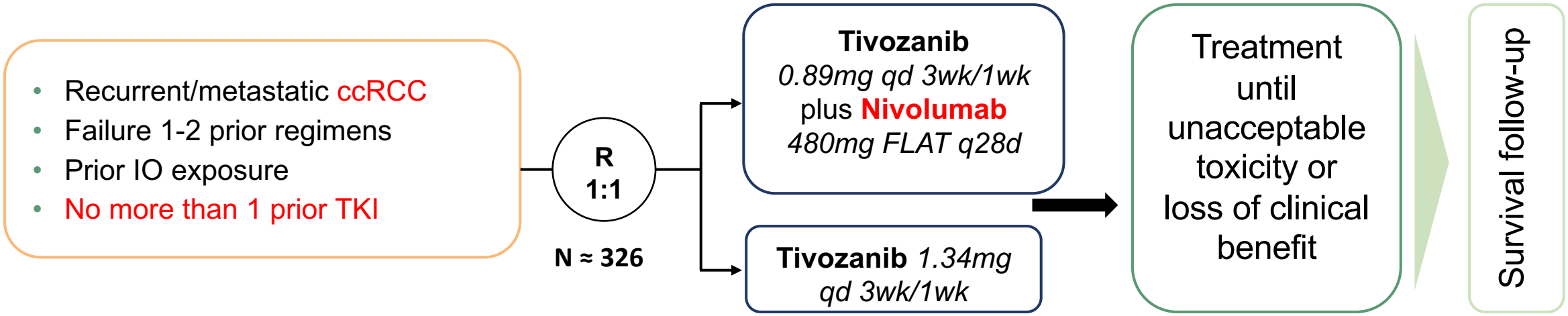


Number at risk

Atezo + Cabo	263	253	226	188	158	133	100	68	43	22	7	6	2	1
Cabo	259	242	216	183	153	130	109	71	52	34	12	8	5	1

[a] Stratified for IMDC risk group. [b] Not significant at α=0.02.

TiNivo2 – Ongoing Phase 3 study (the PD-1 alternative)



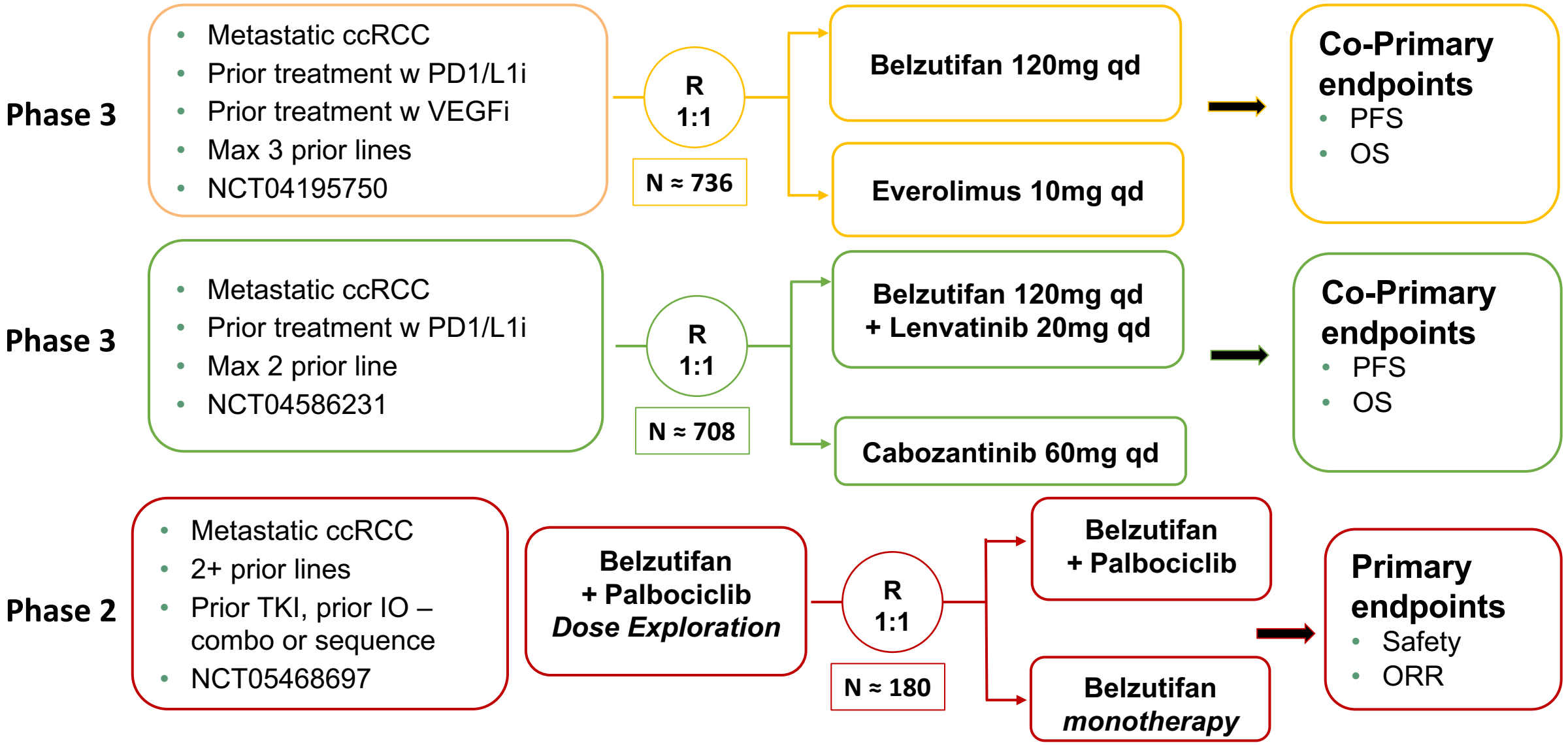
Stratification factors
- IO given immediately prior (y/n)
- IMDC prognostic score

Primary endpoints
- PFS

Additional endpoints
- OS, ORR, DoR, Safety

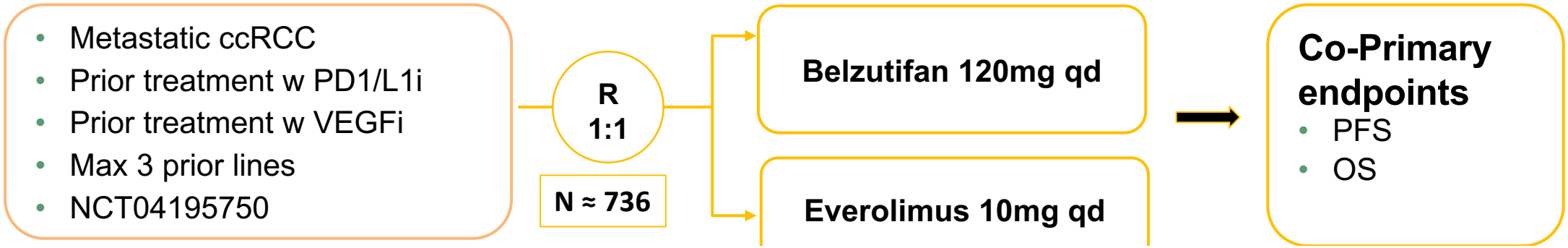
TKI, tyrosine kinase inhibitor; ccRCC, clear cell renal cell carcinoma; DOR, duration of response; IO, immune oncology therapy IMDC, International Metastatic RCC Database Consortium; INV, investigator; IRF, independent review facility; RECIST, Response evaluation criteria in solid tumors

The Post-PD-1 setting using novel agents/targets: HIF-2 inhibitors



The Post-PD-1 setting using novel agents/targets: HIF-2 inhibitors

Phase 3



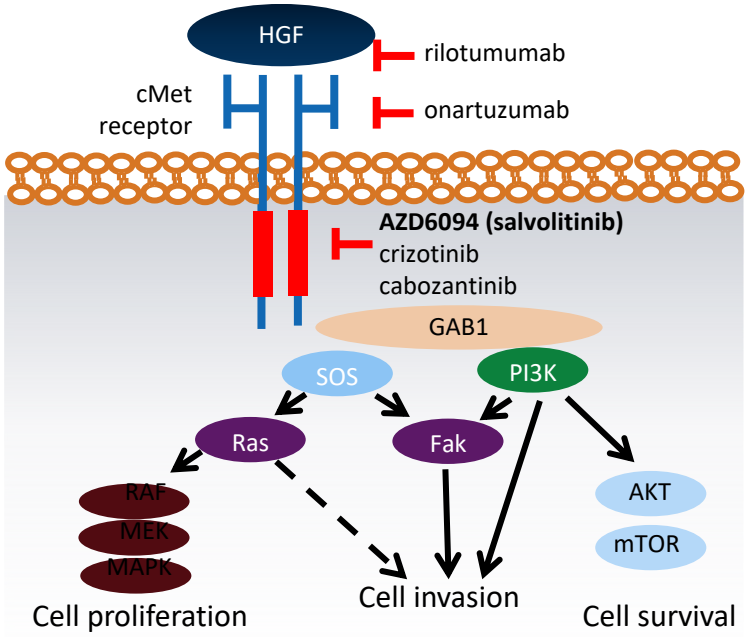
Some Facts about today's RCC landscape:
What worked and what did not work

- 1L metastatic ccRCC
- The de-facto post PD-1 setting
- The non-clear cell RCC setting: The MET story in papillary RCC
- The adjuvant setting

Targeting MET in Papillary RCC

- MET pathway is activated in Papillary RCC:
  - MET alterations (30-40%)
- Savolitinib is a selective small molecule inhibitor of MET

- Phase 2 with MET pathways analyses (N=109)
  - ORR: 7%,
  - In patients with MET alterations: ORR 18% (vs. 0% in MET-independent PRCC.
    - Tumor shrinkage: 61% of patients with MET-driven vs. 20% with MET-independent
  - PFS: 6.2 m vs 1.4 months



- Phase 3 SAVOIR vs. sunitinib in MET-altered patients (N=180):
  - TAA for MET testing was slow
  - IO integration was needed
  - Slow accrual
  - Closed after 60 patients

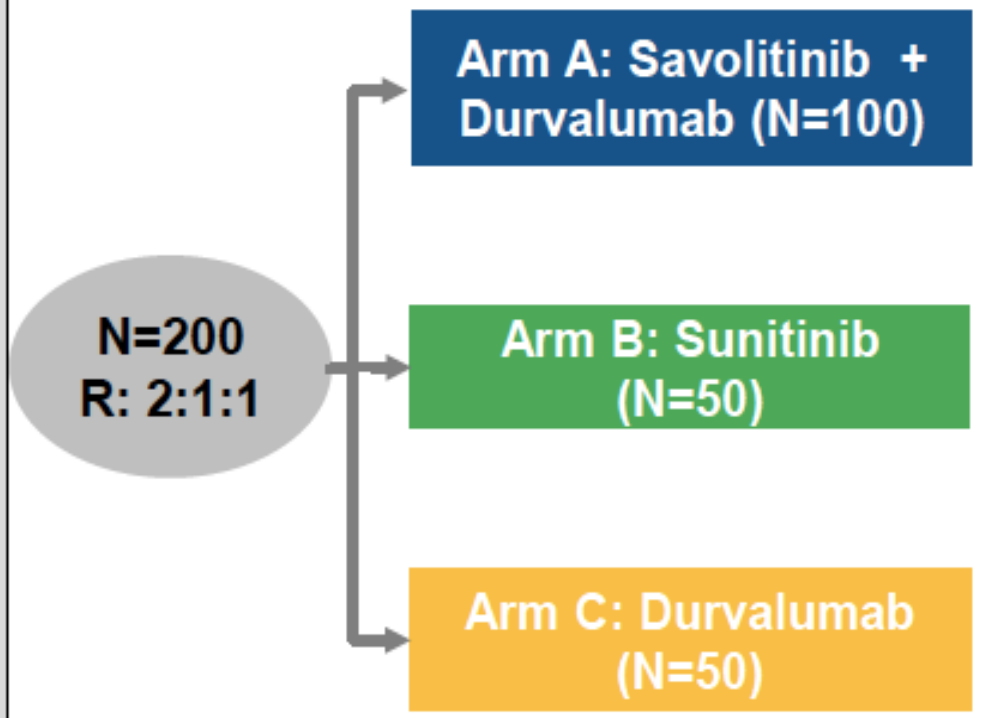
Choueiri TK, et al, *J Clin Oncol*. 2017 and *JAMA Oncol* 2020

SAMETA Study (NCT05043090)

A Phase III, Open Label, Randomised, 3-Arm, Multi-Centre Study of Savolitinib plus Durvalumab versus Sunitinib and Durvalumab Monotherapy in Participants with MET-Driven, Unresectable and Locally Advanced or Metastatic Papillary Renal Cell Carcinoma (PRCC)

Key Eligibility Criteria

- Locally advanced or metastatic PRCC
- Confirmation of MET-driven PRCC without co-occurring FH mutations using central laboratory validated NGS Assay
- 1L patients (Tx naïve in metastatic setting)
- No prior METi, durvalumab or sunitinib
- Measurable disease per RECIST1.1
- Karnofsky Score >70
- Stable/asymptomatic brain mets permitted
- No history of serious liver disease, no active or recent clinically significant cardiac conditions, no active infection, autoimmune or inflammatory disorders*



Primary Endpoint

- PFS by BICR per RECIST 1.1 (Arm A vs. B)

Main Secondary Endpoints

- OS
- ORR, DoR, DCR by BICR
- PFS2
- Safety
- PRO/HRQoL
- Pharmacokinetics

- Savolitinib oral 600mg QD; Durvalumab IV 1500 mg Q4W; Sunitinib oral 50 mg QD (4weeks on/ 2week off).
- Study treatment until disease progression, unacceptable toxicity, or patient withdrawal
- Participants randomized to durvalumab monotherapy arm will be eligible to switch to receive savolitinib in combination with durvalumab at the time of PD

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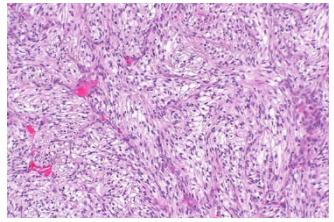
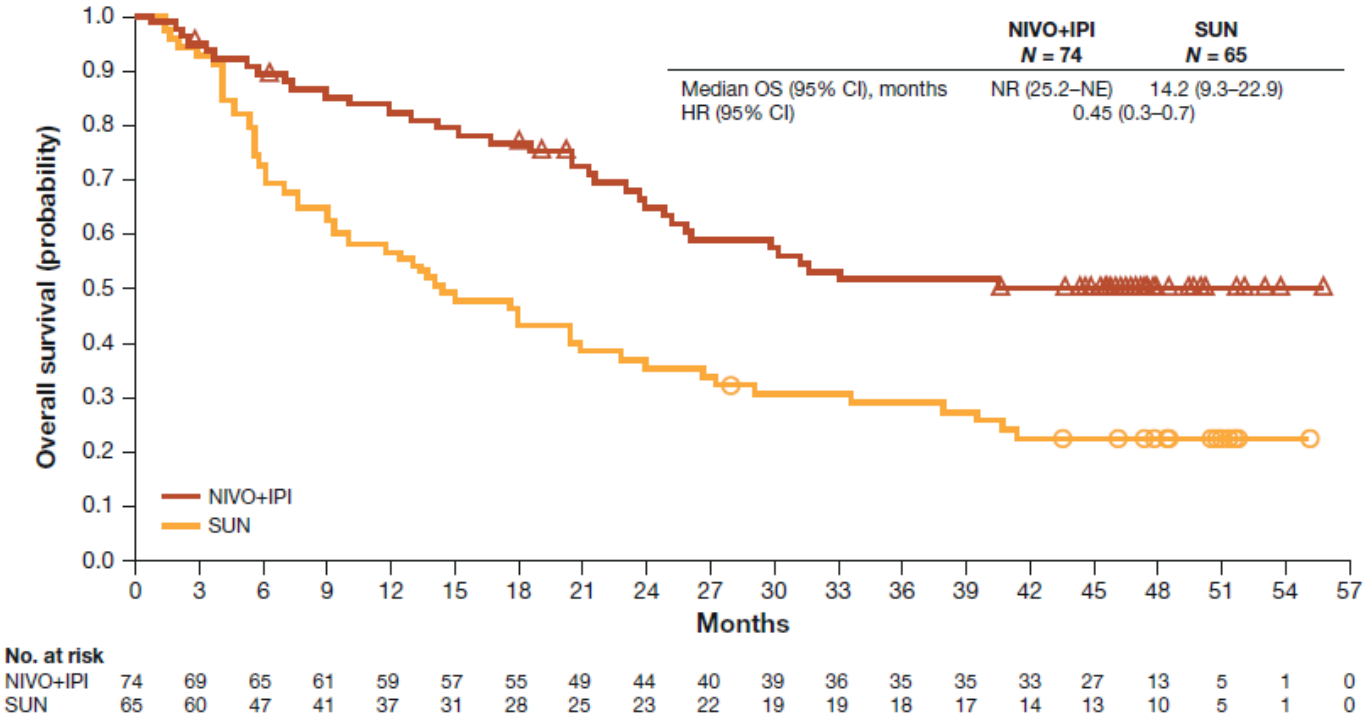
IO + IO in mRCC with Sarcomatoid Features (CheckMate-214)





I/P mRCC	Nivo/Ipi (n=74)	Sunitinib (N=65)	HR
mOS (mo)	NR	14.2	0.45
mPFS (mo)	26.5	5.1	0.56
CR (%)	19	3	

Sarcomatoid RCC tumors are characterized by an *immune-inflamed phenotype*[2]:

1) Activation of immune pathways
2) Increased expression of APM genes
3) Increased cytotoxic immune infiltration
4) High PD-L1 on tumor cells

1. Tannir N. et al., *Clin Cancer Res.*, 2021. PMID: 32873572. 2. Bakouny Z. et al, *Nat Commun.*, 2021. PMID: 33547292.

nature COMMUNICATIONS

Integrative molecular characterization of sarcomatoid and rhabdoid renal cell carcinoma **2021**

Ziad Bakouny[1], David A. Braun[1], Sachet A. Shukla[2], Wenting Pan[1], Xin Gao[3], Yue Hou[2], Abdallah Flaifel[4], Stephen Tang[1], Alice Bosma-Moody[1], Meng Xiao He[1], Natalie Vokes[1], Jackson Nyman[1], Wanling Xie[5], Amin H. Nassar[1], Sarah Abou Alaiwi[1], Ronan Flippot[1], Gabrielle Bouchard[1], John A. Steinharter[1], Pier Vitale Nuzzo[1], Miriam Ficial[4], Miriam Sant'Angelo[4], Juliet Forman[1,2,6], Jacob E. Berchuck[1], Shaan Dudani[7], Kevin Bi[1], Jihye Park[1], Sabrina Camp[1], Maura Sticco-Ivins[4], Laure Hirsch[1], Sylvan C. Baca[1], Megan Wind-Rotolo[8], Petra Ross-Macdonald[8], Maxine Sun[1], Gwo-Shu Mary Lee[1], Steven L. Chang[1], Xiao X. Wei[1], Bradley A. McGregor[1], Lauren C. Harshman[1], Giannicola Genovese[9], Leigh Ellis[4,10], Mark Pomerantz[1], Michelle S. Hirsch[4], Matthew L. Freedman[1], Michael B. Atkins[11], Catherine J. Wu[1,6], Thai H. Ho[12], W. Marston Linehan[13], David F. McDermott[14], Daniel Y. C. Heng[7], Srinivas R. Viswanathan[1], Sabina Signoretti[4,10], Eliezer M. Van Allen[1,15✉] & Toni K. Choueiri[1,15✉]

Some Facts about today's RCC landscape: What worked and what did not work

- 1L metastatic ccRCC
- The de-facto post PD-1 setting
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The Landscape of Adjuvant immune checkpoint studies in RCC

Trial	Sample Size	Inclusion Criteria	Treatment	Duration	Primary Endpoint	Met Primary Endpoint?
KEYNOTE-564	994	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED within 1 year); clear cell	Pembrolizumab vs placebo	12 months	DFS	
IMmotion010	778	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED*); clear cell	Atezolizumab vs placebo	12 months	DFS	
CheckMate-914	1,600	pT2aG3-4N0, pT2b-T4GxN0, pTxGxN1; clear cell	Nivolumab + ipilimumab vs nivolumab + placebo vs placebo	6 months	DFS	
PROSPER	766	T2Nx, TxN1, TxNxM1 (resected to NED); any RCC histology	Nivolumab vs active monitoring	10 doses total (1 preop)	EFS	
RAMPART	1,750	Leibovich score 3-11; any RCC histology	Durvalumab + tremelimumab vs durvalumab vs active monitoring	12 months	DFS, OS	Accruing 7/2024
LITESPARK-022	1,600	pT2G4/sarcomatoid, pT3, pT4, pTxN1, pTxNxM1 (resected to NED) clear cell	Belzutifan + pembrolizumab vs pembrolizumab	12 months	DFS	Accruing

*Metachronous pulmonary, lymph node, or soft tissue recurrence >12 months from nephrectomy
CPI = checkpoint inhibitors; EFS = event-free survival; NED = no evidence of disease; OS = overall survival.

Next steps in the Adjuvant RCC Landscape

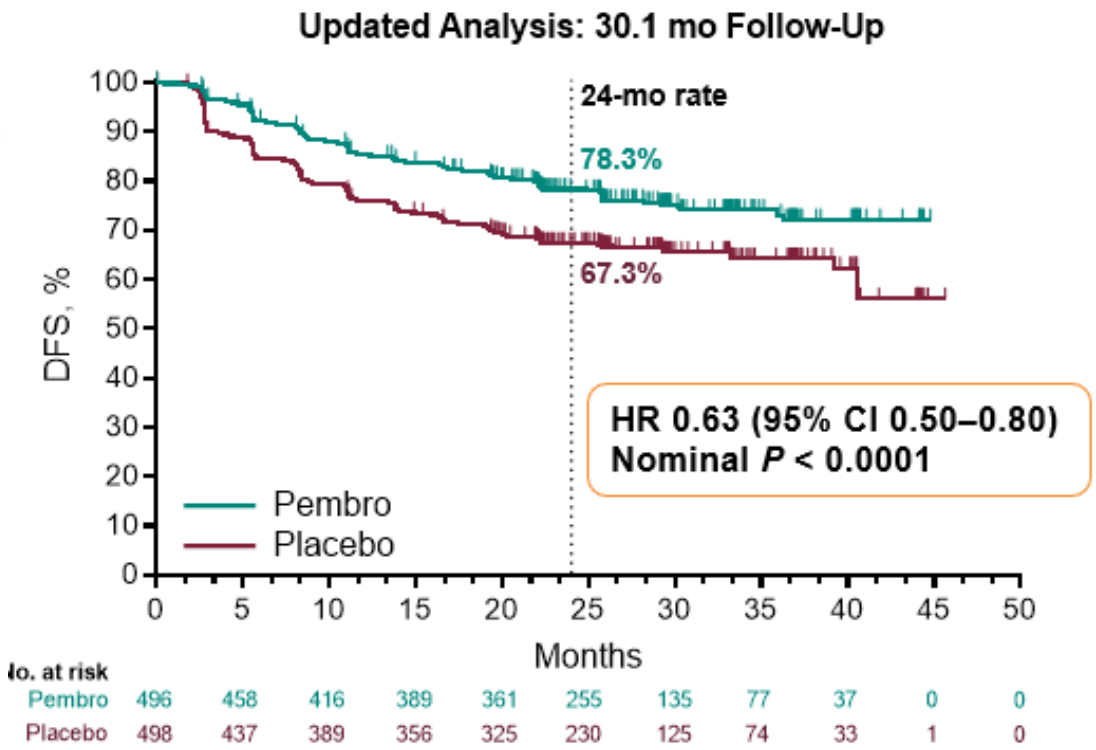
Traditional model of trials: 1 vs. 1+2

The NEW ENGLAND JOURNAL of MEDICINE

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

Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma

T.K. Choueiri, P. Tomczak, S.H. Park, B. Venugopal, T. Ferguson, Y.-H. Chang, J. Hajek, S.N. Symeonides, J.L. Lee, N. Sarwar, A. Thiery-Vuillemin, M. Gross-Goupil, M. Mahave, N.B. Haas, P. Sawrycki, H. Gurney, C. Chevreau, B. Melichar, E. Kopyltsov, A. Alva, J.M. Burke, G. Doshi, D. Topart, S. Oudard, H. Hammers, H. Kitamura, J. Bedke, R.F. Perini, P. Zhang, K. Imai, J. Willemann-Rogerio, D.I. Quinn, and T. Powles, for the KEYNOTE-564 Investigators*



	Pts w/ Event	Median, mo (95% CI)
Pembro	114	NR (NR–NR)
Placebo	169	NR (40.5–NR)

LITESPARK-022: Belzutifan + Pembro for Adjuvant RCC

Key Eligibility Criteria:

- Histologically confirmed diagnosis of ccRCC
  - **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 (≤ 2 yrs from nephrectomy)
- Complete resection of primary tumor (partial or radical nephrectomy) and metastatic lesions (for M1 NED pts)
- Randomized ≤ 12 wks after surgery
- ECOG PS 0-1
- No preexisting brain or bone metastatic lesions
- No prior systemic therapy or radiotherapy for RCC

N = 1600
1:1 (blinded)

Belzutifan (120 mg QD ~12 mo) + **Pembrolizumab** (400 mg Q6W x 9 cycles)
N=800

Placebo (QD ~12 mo) + **Pembrolizumab** (400 mg Q6W x 9 cycles)
N=800

Primary endpoint:

- DFS by Investigator

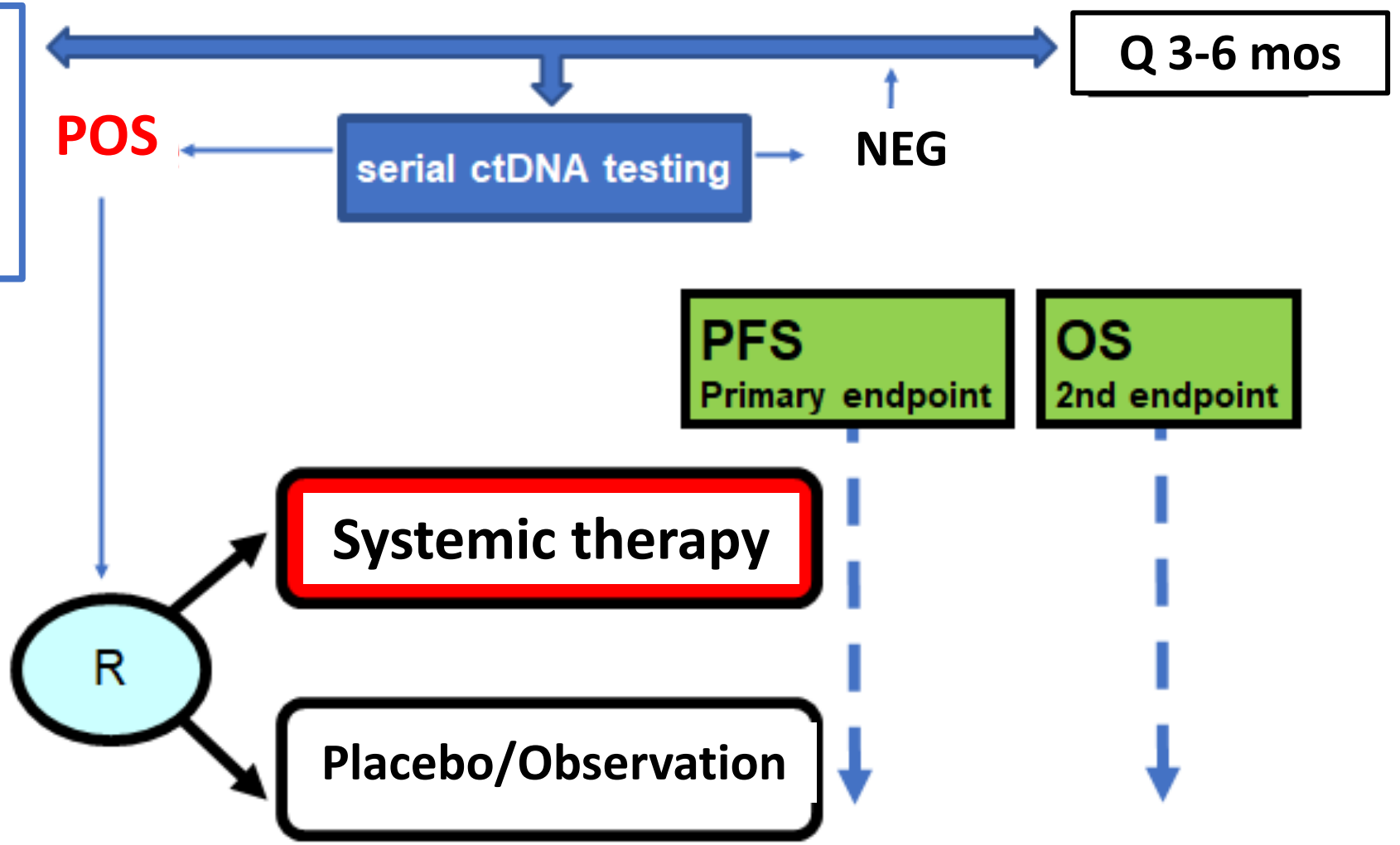
Secondary endpoints:

- OS, safety, disease recurrence-specific survival, and PROs

ClinicalTrials.gov Identifier: NCT05239728

A Rational approach to Clinical trial design for adjuvant RCC

Post-Nephrectomy for High-Risk RCC

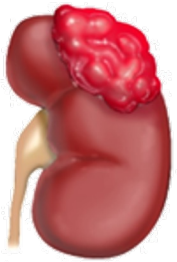


RCC does not shed much ctDNA!

Personalized vaccine for High-Risk RCC

NEOVAX TRIAL in High-Risk RCC

Tumor procurement	Target selection	Personal vaccine manufacture	Vaccine administration



ccRCC
Stage III-IV

No evidence of disease after surgery

WES, RNAseq

Prediction of personal neoAgs via HLAthena

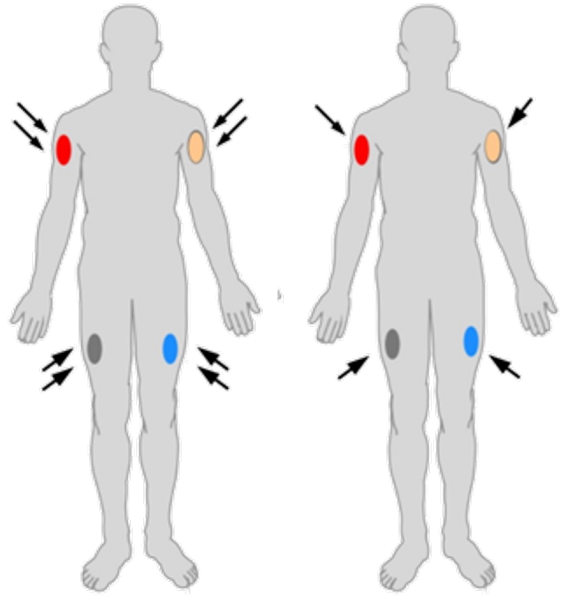
Pools of synthetic long peptides

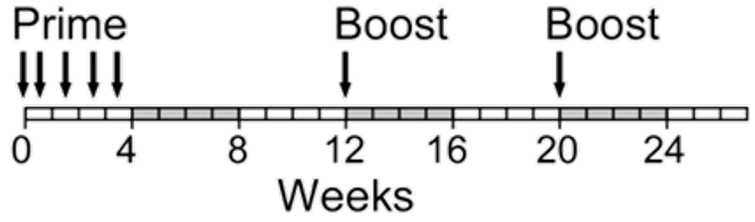
+ poly ICLC

+/- Local ipilimumab

Cohort 1
+ ipilimumab
(n=5)

Cohort 2
- ipilimumab
(n=4)



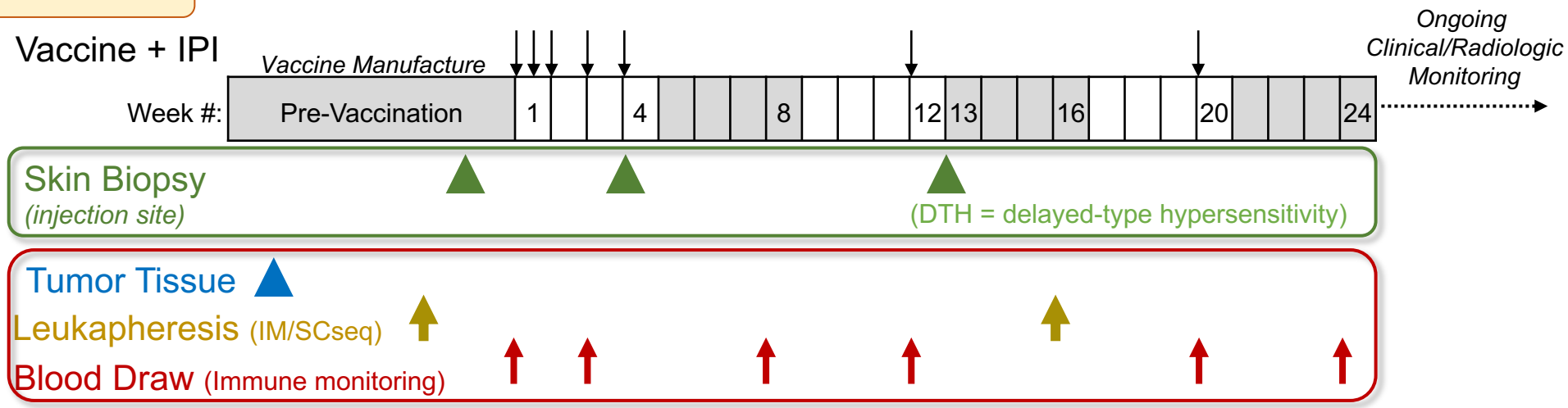


Administered 1/2 s.c., 1/2 i.d.

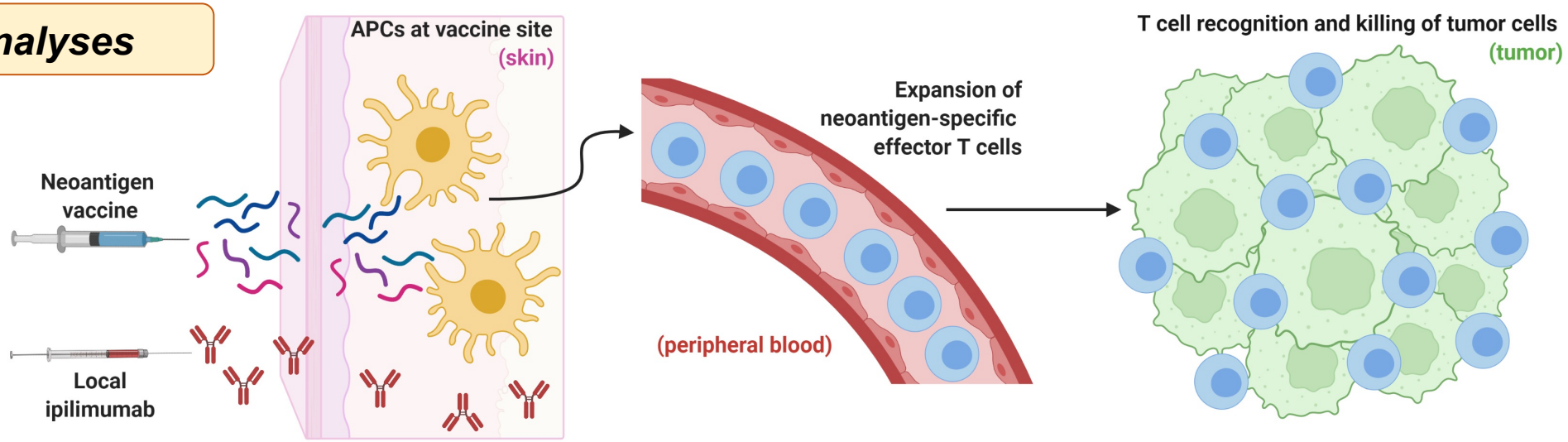
NCT02950766
PI: Choueiri/Ott/Braun

Assessing neoantigen vaccine responses

Biospecimen collection

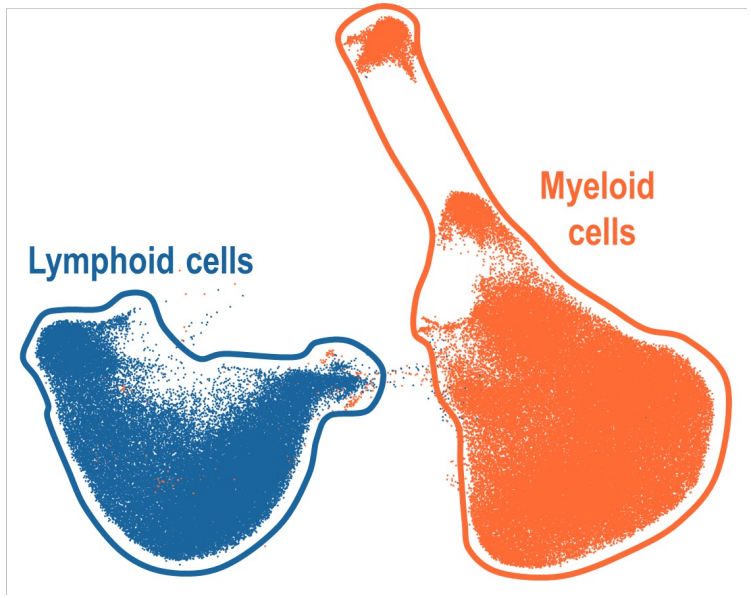


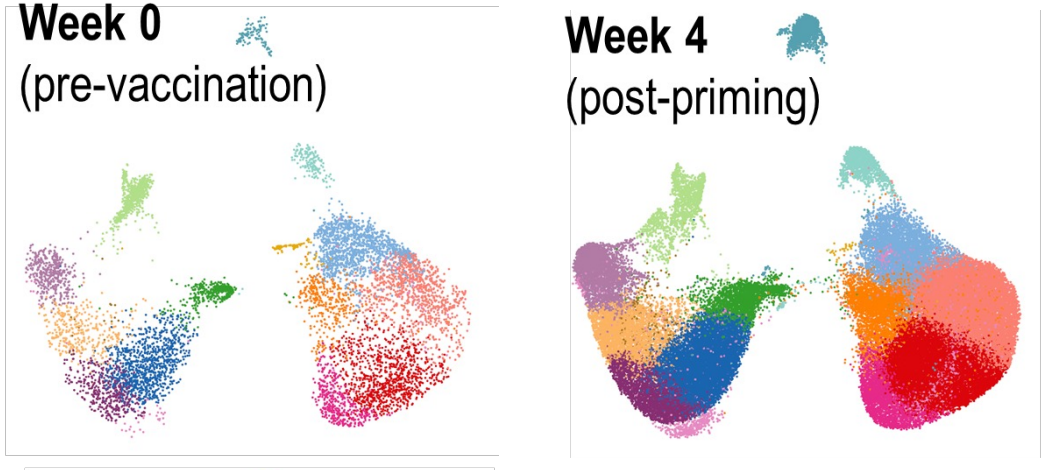
Planned analyses



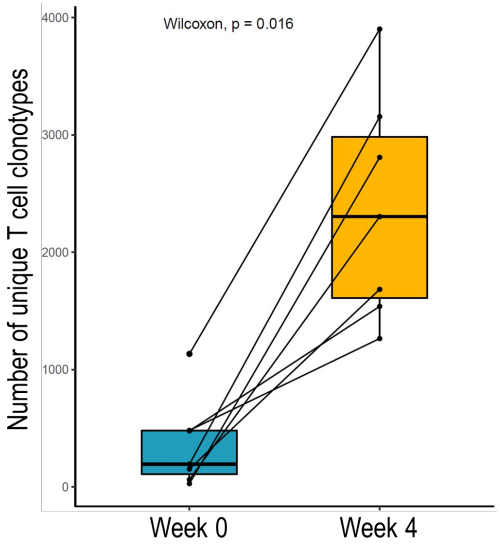
scRNA-seq analysis of vaccine site skin reveals changes in immune composition (Prelim: unpublished)

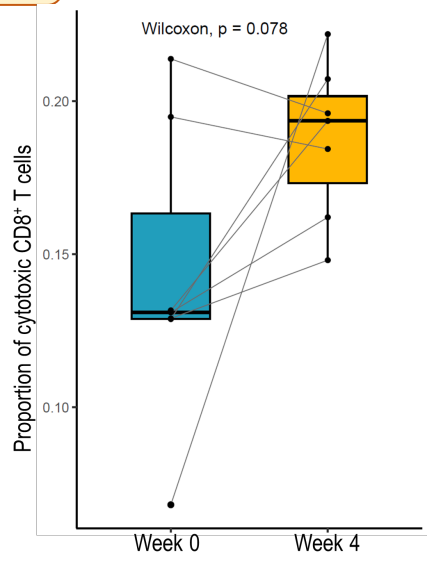
Immune infiltration increases with vaccination

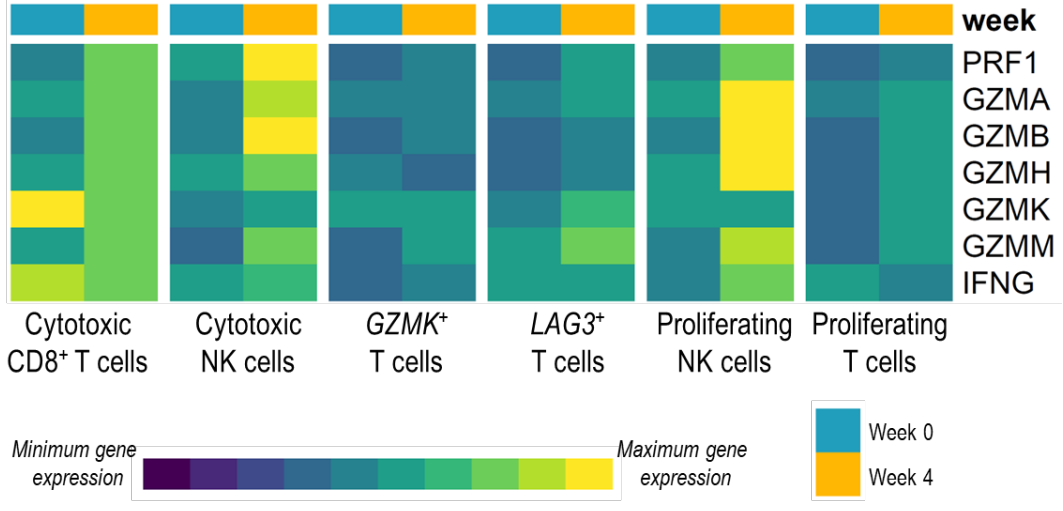




Impact of vaccine







One slide summary: RCC in 2023 and beyond

- Strong science was celebrated in 2018 and 2019 *(pre-covid)* through the story of immune checkpoints and the oxygen sensing VEGF/HIF2 pathways.

→ **RCC is an obvious clinical application for 2018 and 2019 Nobel Prizes**

- Clinical trials designs in RCC are evolving:
  - Additive, adaptative, sequential, organ-based, Biomarker-based (Think SAMETA)
  - The adjuvant setting is a fertile ground for new trial designs because we overtreat patients
  - New targets/drugs that work **>** new designs every day

- This is *just* the beginning in ccRCC; median OS 1L metastatic RCC:
  - A trial in 2000[1]: 15 months
  - A trial in 2015[2] : 25 months
  - A trial in 2018[3]: 56 months

1. Motzer R.J. et al., *JCO*, 2000. PMID: 10944130
2. Motzer R.J. et al., *NEJM*, 2015. PMID: 26406148
3. Albiges L. et al., *ESMO Open*, 2020. PMID: 33246931

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- Wu Lab
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- **Freeman lab**
- **Sharpe Lab**
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- Romee Lab
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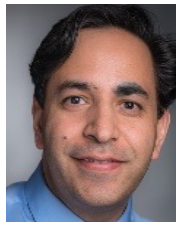
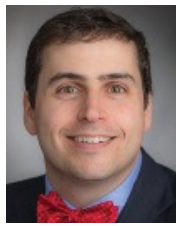
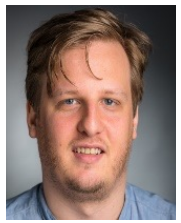
- Nursing/clinical/research teams
- Industry partners
- Many others…



The Patients

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NCI SPORE P50 CA101942

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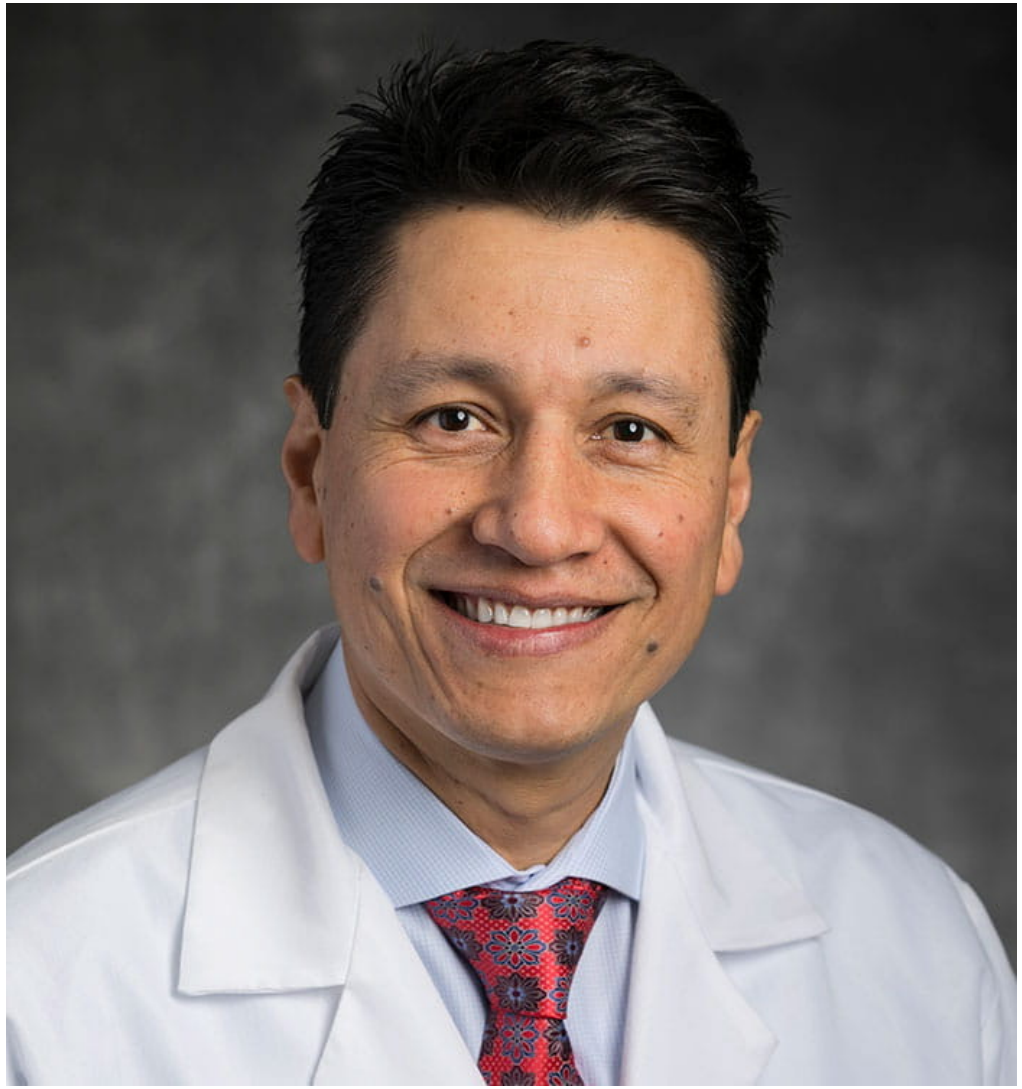

Jorge Garcia, MD

Phase II Study of Lenalidomide in Patients With Metastatic Renal Cell Carcinoma

2004-2005

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BACKGROUND. Lenalidomide (LEN) is a structural and functional analogue of thalidomide that has demonstrated enhanced immunomodulatory properties and a more favorable toxicity profile. A Phase II, open-label study of LEN in patients with metastatic renal cell carcinoma (RCC) was conducted to determine its safety and clinical activity.

METHODS. Patients with metastatic RCC received LEN orally at a dose of 25 mg daily for the first 21 days of a 28-day cycle. The primary endpoint was the objective response rate. Time to treatment failure, safety, and survival were secondary endpoints.

RESULTS. In total, 28 patients participated in the trial and were included in the current analysis. Three of 28 patients (11%) demonstrated partial responses and continued to be progression-free for >15 months. Eleven patients (39%) had stable disease that lasted >3 months, including 8 patients who had tumor shrinkage. In total, 6 patients (21%) remained on the trial, and 5 additional patients continued to be followed for survival. The median follow-up for those 11 patients was 13.5 months (range, 8.3–17.0 months). The median survival had not been reached at the time of the current report. Serious adverse events included fatigue (11%), skin toxicity (11%), and neutropenia (36%).

CONCLUSIONS. LEN demonstrated an antitumor effect in metastatic RCC, as evidenced by durable partial responses. LEN toxicities were manageable. Further studies will be required to assess the overall activity of LEN in patients with metastatic RCC. ***Cancer* 2006;107:2609–16.** © *2006 American Cancer Society.*

Cancer

2007-2009

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A phase 2, single-arm study of ramucirumab in patients with metastatic renal cell carcinoma with disease progression on or intolerance to tyrosine kinase inhibitor therapy

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