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Overview of the ongoing clinical trials in renal cell cancer

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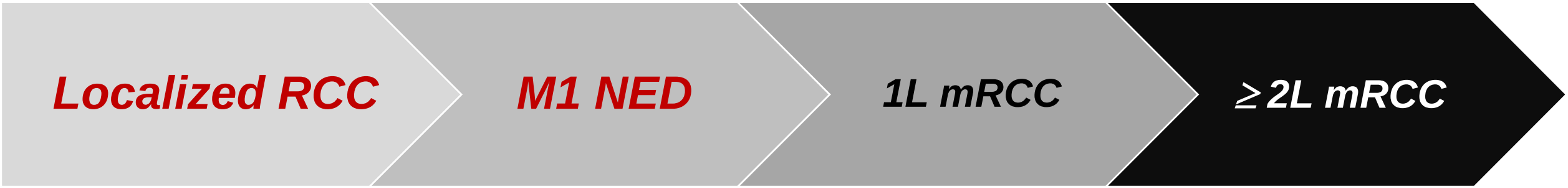
- Travel expenses: Janssen
- Speaker compensation: Merck

Clear cell renal cell carcinoma

Localized RCC → ***M1 NED*** → ***1L mRCC*** → ***≥2L mRCC***

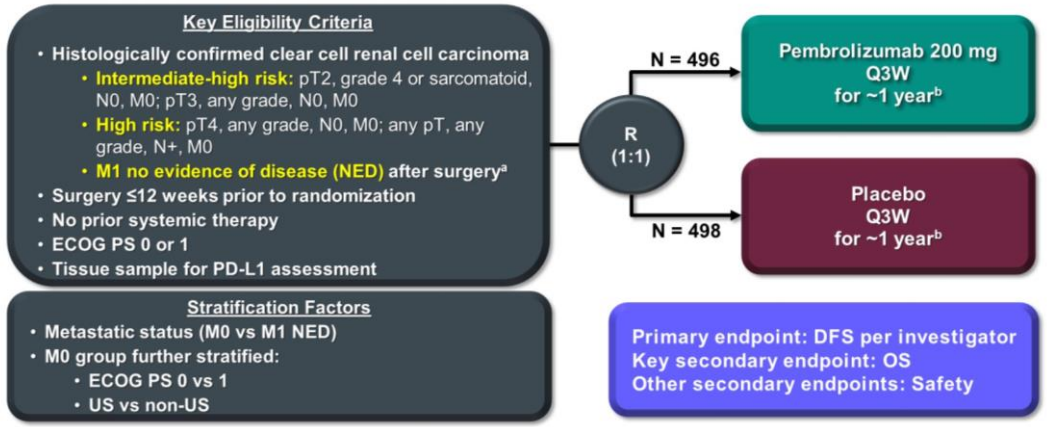
Clear cell renal cell carcinoma



Adjuvant setting – ccRCC

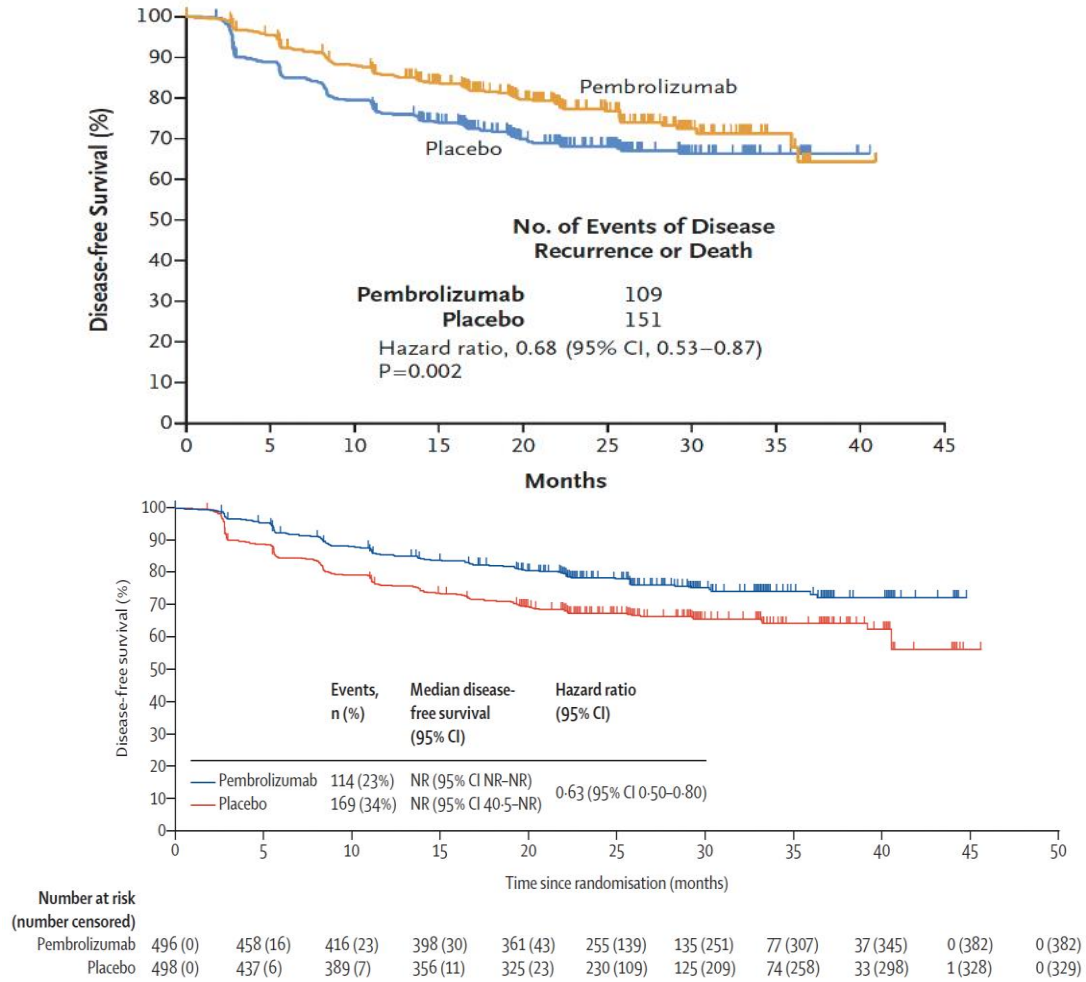
Landmark KEYNOTE-564 trial in high-risk RCC

(with 30-month follow-up update)



Approved Nov 17, 2021

Approved Jan 27, 2022



Choueiri TK, et al. *N Engl J Med*. 2021 Aug 19;385(8):683-694; Powles T, et al. *Lancet Oncol*. 2022 Sep;23(9):1133-1144

Adjuvant setting – ccRCC

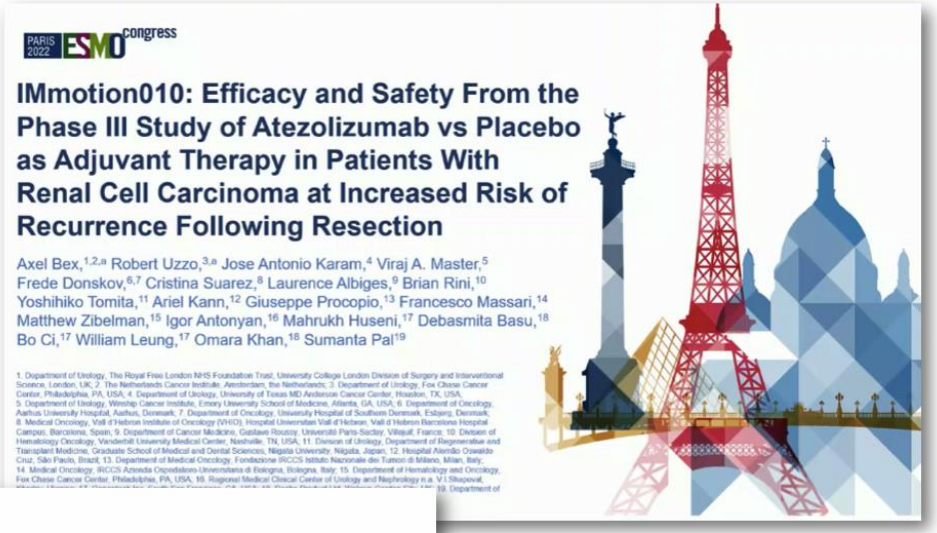
Latest news from ESMO 2022…


PARIS 2022 ESMO congress

Phase III RandOmized Study Comparing PErioperative Nivolumab (Nivo) versus Observation in Patients with Renal Cell Carcinoma Undergoing Nephrectomy (PROSPER, ECOG-ACRIN EA8143), a National Clinical Trials Network trial

Mohamad E Allaf, MD

Director and Urologist-in-Chief
Johns Hopkins University, Baltimore, Maryland, USA
September 10, 2022


PARIS 2022 ESMO congress

IMmotion010: Efficacy and Safety From the Phase III Study of Atezolizumab vs Placebo as Adjuvant Therapy in Patients With Renal Cell Carcinoma at Increased Risk of Recurrence Following Resection

Axel Bex,[1,2,a] Robert Uzzo,[3,a] Jose Antonio Karam,[4] Viraj A. Master,[5] Frede Donskov,[6,7] Cristina Suarez,[8] Laurence Albiges,[9] Brian Rini,[10] Yoshihiko Tomita,[11] Ariel Kann,[12] Giuseppe Procopio,[13] Francesco Massari,[14] Matthew Zibelman,[15] Igor Antonyan,[16] Mahrukh Huseni,[17] Debasmita Basu,[18] Bo Ci,[17] William Leung,[17] Omara Khan,[18] Sumanta Pal[19]


PARIS 2022 ESMO congress

Adjuvant nivolumab plus ipilimumab versus placebo for localized renal cell carcinoma at high risk of relapse after nephrectomy: results from the randomized, phase 3 CheckMate 914 trial

Robert J. Motzer,[1] Paul Russo,[1] Viktor Grünwald,[2] Yoshihiko Tomita,[3] Bogdan Zurawski,[4] Omi Parikh,[5] Sebastiano Buti,[6] Philippe Barthélémy,[7] Jeffrey C. Goh,[8] Dingwei Ye,[9] Alejo Lingua,[10] Jean-Baptiste Lattouf,[11] Bernard Escudier,[12] Saby George,[13] Brian Shuch,[14] Burcin Simsek,[15] Julia Spiridigliozzi,[15] Aleksander Chudnovsky,[15] Axel Bex[16]

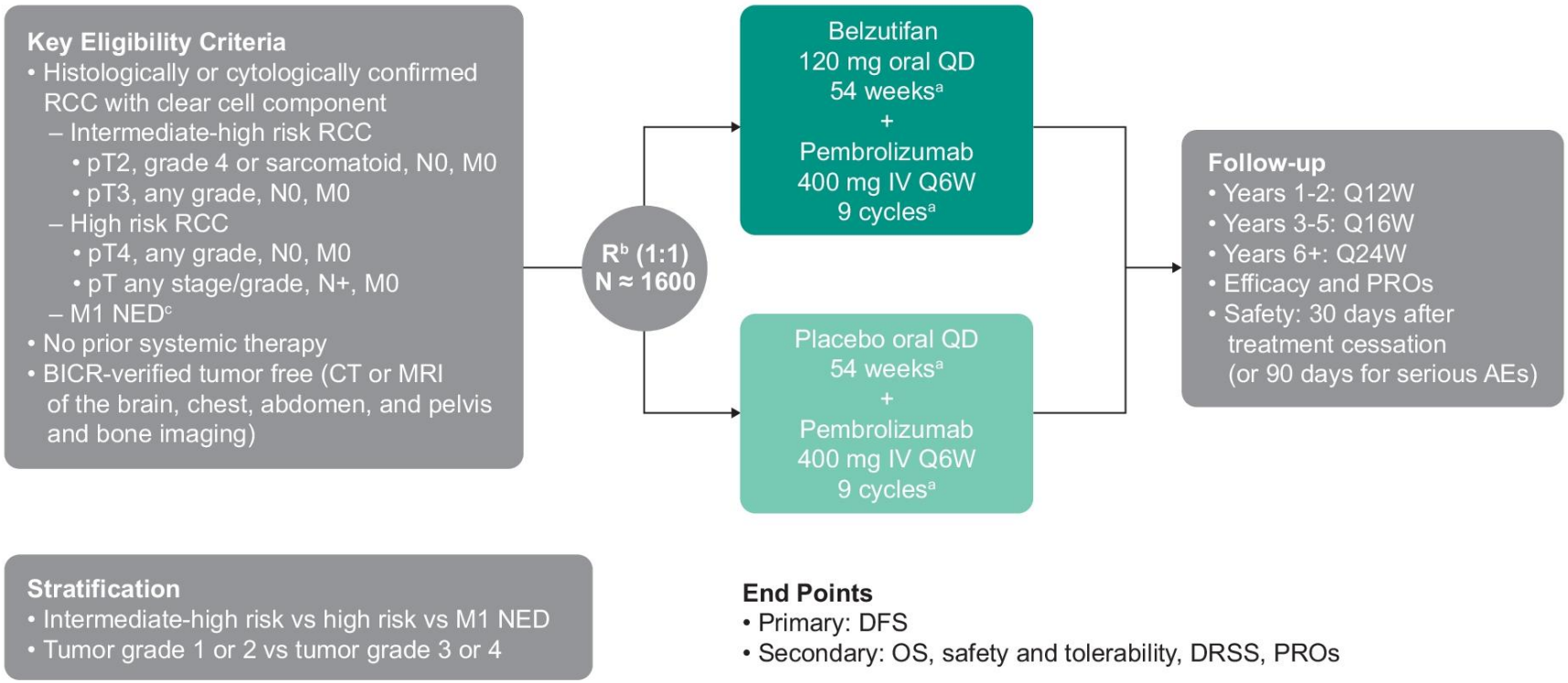
[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]West-German Cancer Center Essen, University Hospital Essen, Essen, Germany; [3]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [4]Prof. Franciszek Lukaszczyk Oncology Centre, Bydgoszcz, Poland; [5]Rosemere Cancer Centre, Lancashire Teaching Hospitals NHS Trust, Preston, UK; [6]University Hospital of Parma, University of Parma, Parma, Italy; [7]Institut de Cancérologie Strasbourg Europe, Strasbourg, France; [8]Royal Brisbane and Women's Hospital, Herston, QLD, Australia; [9]Fudan University Shanghai Cancer Center, Shanghai, China; [10]Instituto Médico Río Cuarto, Río Cuarto, Argentina; [11]CHUM - Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; [12]Gustave Roussy, Villejuif, France; [13]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [14]University of California, Los Angeles, Los Angeles, CA, USA; [15]Bristol Myers Squibb, Princeton, NJ, USA; [16]Netherlands Cancer Institute, Amsterdam, the Netherlands

Presentation number: LBA4

3 negative trials!

Adjuvant setting – ccRCC: LITESPARK-022

A Multicenter, Double-blind, Randomized Phase 3 Study to Compare the Efficacy and Safety of Belzutifan (MK-6482) Plus Pembrolizumab (MK-3475) Versus Placebo Plus Pembrolizumab, in the Adjuvant Treatment of Clear Cell Renal Cell Carcinoma (ccRCC) Post Nephrectomy (MK-6482-022)



AE, adverse event; BICR, blinded independent central review; CT, computed tomography; IV, intravenously; MRI, magnetic resonance imaging; NED, no evidence of disease; QD, once daily; Q6W, every 6 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; Q24W, every 24 weeks; R, randomization.

ClinicalTrials.gov Identifier: NCT05239728

Choueiri T et al., Poster presented at at ASCO 2022

Adjuvant setting – ccRCC: LITESPARK-022

Patient eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • Histologically or cytologically confirmed diagnosis of RCC with clear cell component, with or without sarcomatoid features • Intermediate-high risk, high-risk, or M1 NED RCC[a] • No prior systemic therapy • Nephrectomy and/or metastasectomy ≤12 weeks before randomization • Tumor free as assessed by investigator and verified by BICR by CT or MRI of the brain and CAP (≤28 days from randomization) and bone imaging (≤42 days from randomization) • ECOG PS score of 0 or 1 assessed within 10 days before randomization	• Major surgery within 4 weeks before randomization (other than nephrectomy + resection of preexisting metastases for patients with M1 NED ≤12 weeks) • Pulse oximeter reading <92% at rest, necessitating intermittent or long-term supplemental oxygen • Significant cardiovascular disease within 6 months before first dose of study drug • History of (noninfectious) pneumonitis/interstitial lung disease that necessitated steroids or current pneumonitis/interstitial lung disease • Clinically significant disorders, including serious active nonhealing wound/ulcer/bone fracture, or need for hemodialysis or peritoneal dialysis • Preexisting bone or brain metastatic lesions • Active autoimmune disease that necessitated systemic treatment in the past 2 years • Active infection that necessitates systemic therapy • History of hepatitis B virus or active hepatitis C virus infection

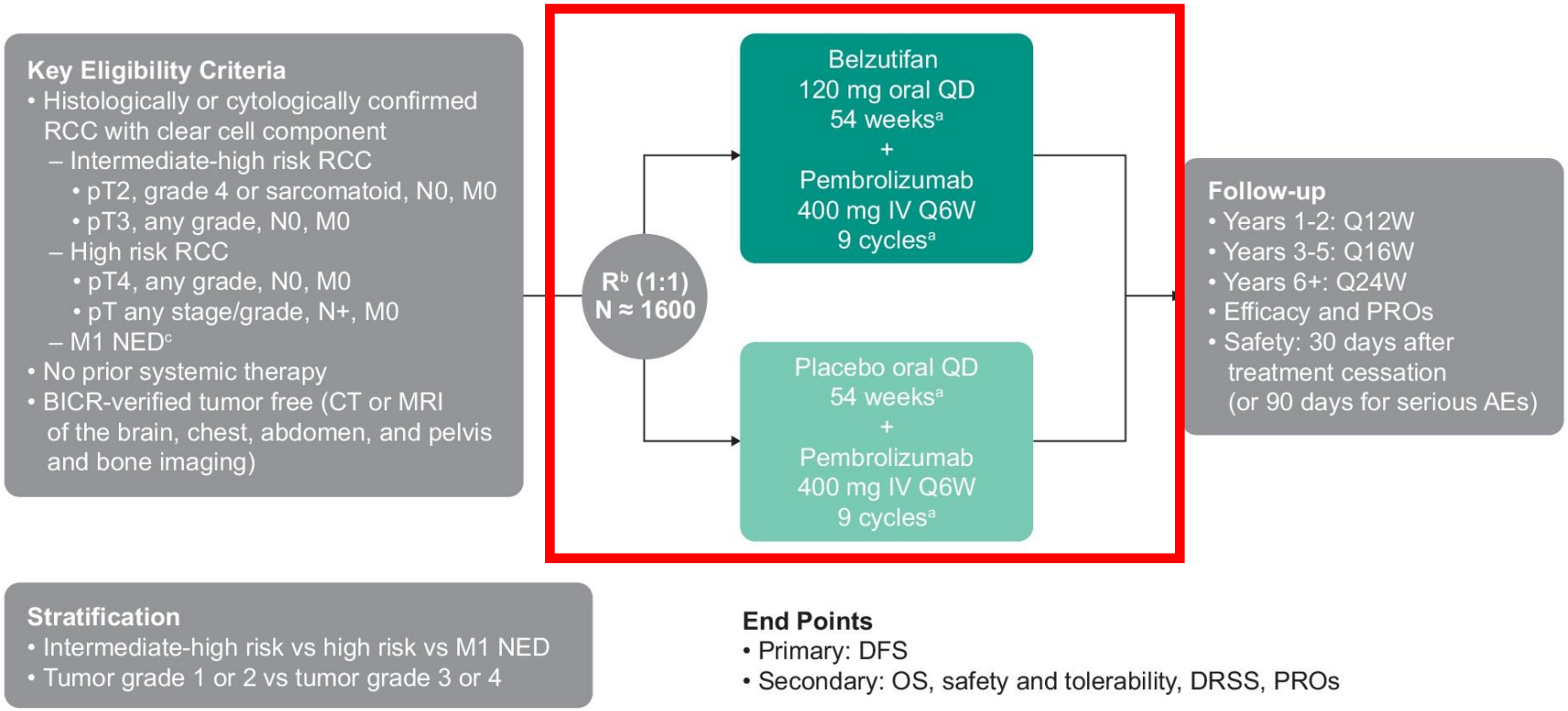
CAP, chest, abdomen, and pelvis; ECOG PS, Eastern Cooperative Oncology Group performance status.

[a]Intermediate- to high-risk RCC (pT2, grade 4 or sarcomatoid, N0, M0, pT3, any grade, N0, M0); high-risk RCC (pT4, any grade, N0, M0, pT, any stage, any grade, N+, M0); M1 NED RCC (patients who initially have a primary kidney tumor and nonbone, nonvisceral, soft tissue metastases that were completely resected at 1 of the following: time of nephrectomy [synchronous] or ≤2 years from nephrectomy [metachronous]).

Choueiri T et al., Poster presented at at ASCO 2022

Adjuvant setting – ccRCC: LITESPARK-022

A Multicenter, Double-blind, Randomized Phase 3 Study to Compare the Efficacy and Safety of Belzutifan (MK-6482) Plus Pembrolizumab (MK-3475) Versus Placebo Plus Pembrolizumab, in the Adjuvant Treatment of Clear Cell Renal Cell Carcinoma (ccRCC) Post Nephrectomy (MK-6482-022)



AE, adverse event; BICR, blinded independent central review; CT, computed tomography; IV, intravenously; MRI, magnetic resonance imaging; NED, no evidence of disease; QD, once daily; Q6W, every 6 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; Q24W, every 24 weeks; R, randomization.

ClinicalTrials.gov Identifier: NCT05239728

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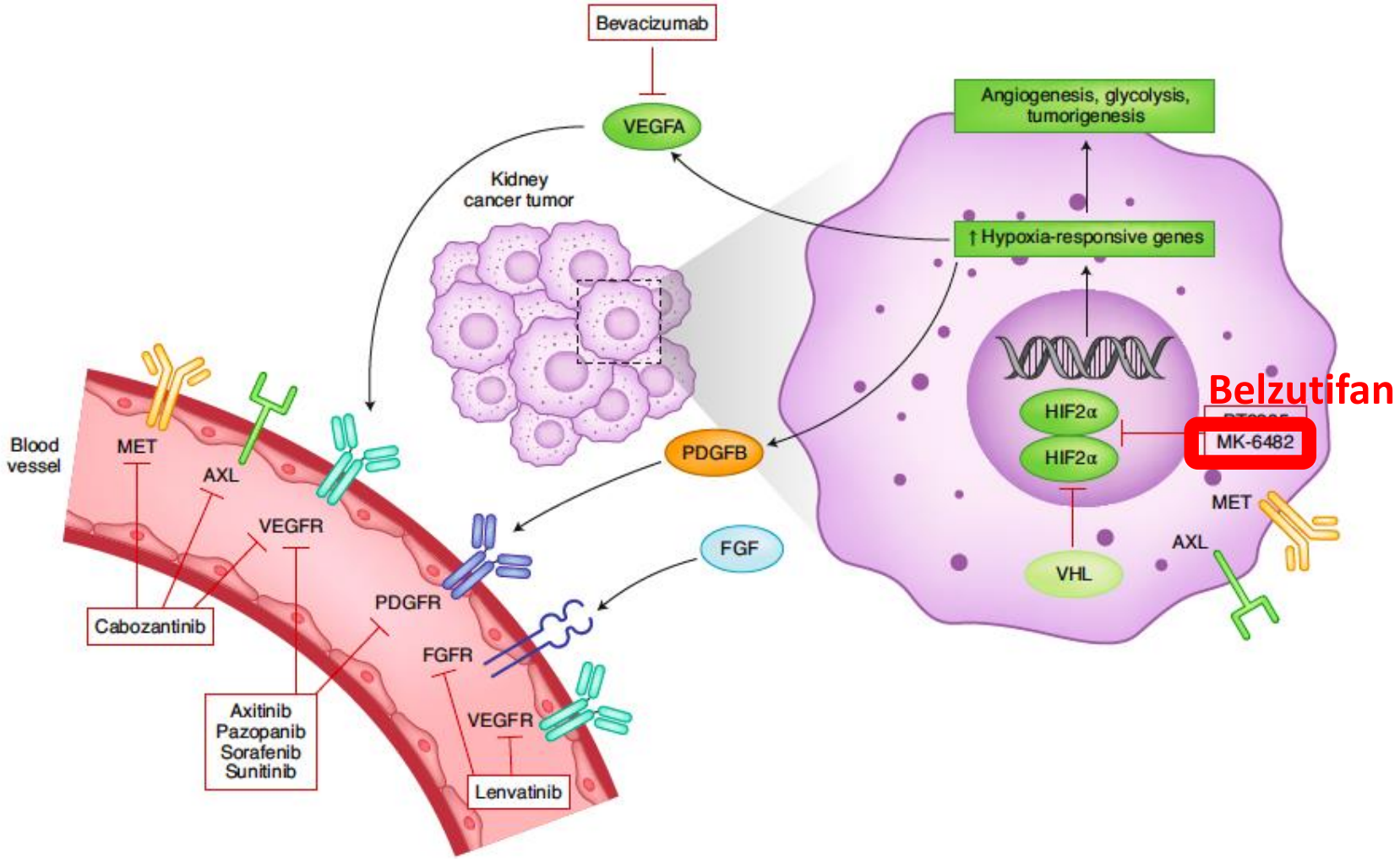
Adjuvant setting – ccRCC: LITESPARK-022



Belzutifan

- Preclinical data indicate that HIF-2α subunit antagonists, which block HIF pathway activation at its **most proximal source**, inhibit tumor growth in clear-cell RCC
- Belzutifan (MK-6482) is a **second-generation small-molecule HIF-2α inhibitor**
- Belzutifan for RCC in VHL disease (MK-6482-004): **ORR 49%**
- Belzutifan for pretreated advanced RCC (NCT02974738): 30 patients (55%) had SD, with a **DCR** (CR+PR+SD) of **80%**

Choueiri T, Kaelin WG, Nat Med 2020; Jonasch E, et al. *N Engl J Med*. 2021, Bauer TM et al, ASGO GU 2021

Adjuvant setting – ccRCC: LITESPARK-022

Primary Hypothesis: Belzutifan plus pembrolizumab is superior to pembrolizumab with respect to disease-free survival (DFS)

Primary endpoint

- **DFS as assessed by investigator**

Secondary endpoints

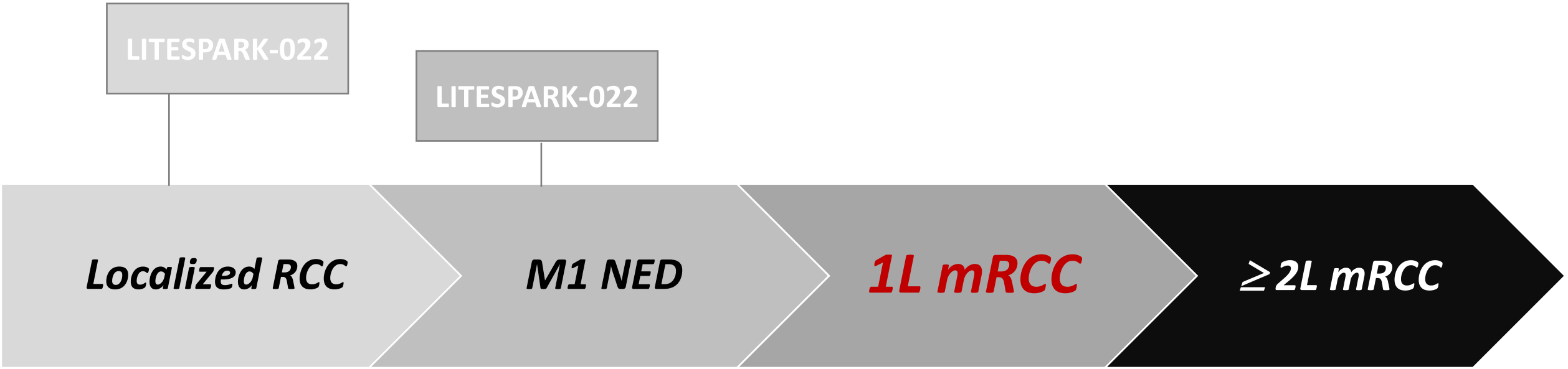
- Overall survival
- Adverse events
- Disease recurrence-specific survival (DRSS)
- PROs (FKSI-DRS, EORTC-QLQ-C30)

Exploratory endpoints

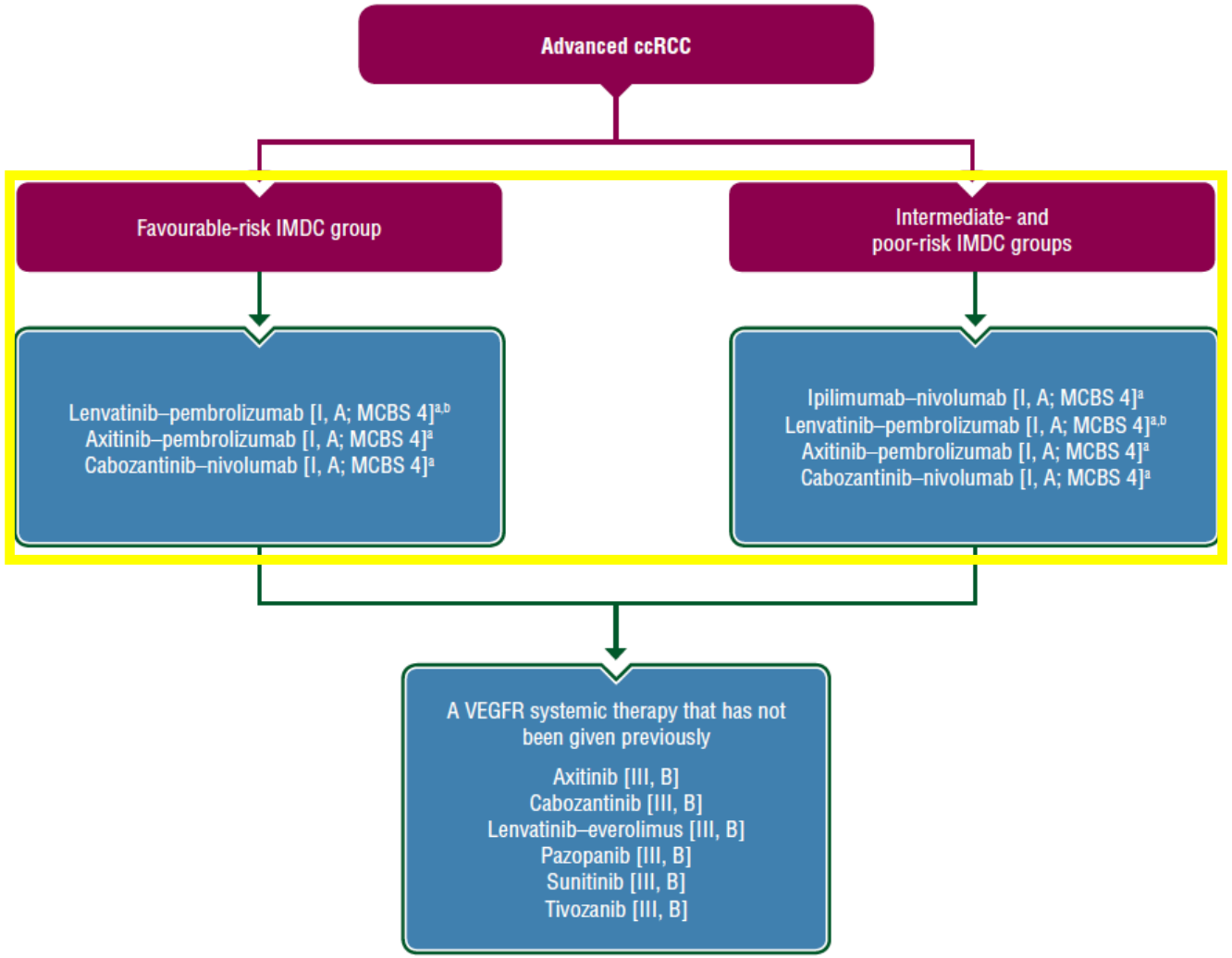
PK belzutifan
PROs (FKSI-DRS, EuroQoL EQ-5D-5L, FACT-G)
Biomarkers

ClinicalTrials.gov Identifier: NCT05239728

Clear cell renal cell carcinoma



Advanced ccRCC – 1st Line



ESMO Guidelines on Renal cell carcinoma, 2021

Advanced ccRCC – 1st Line

Summary of Randomized Phase 3 Trials testing IO-IO and IO-TKI in 1L RCC

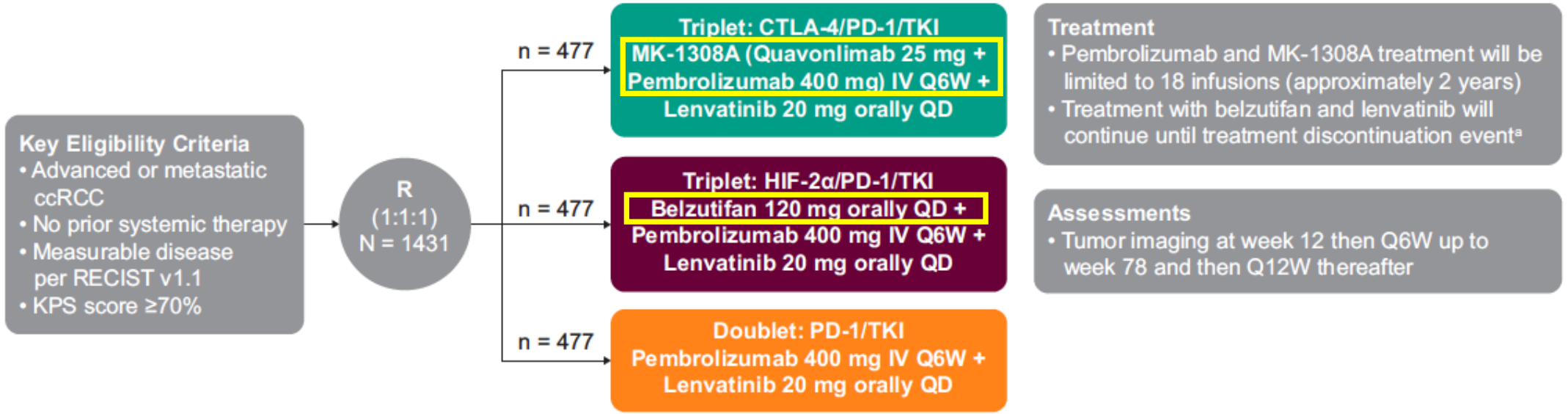
Characteristics	CheckMate 214[1]	KEYNOTE-426[2]	KEYNOTE-581 (CLEAR)[3]	JAVELIN Renal 101[4]	CheckMate 9ER[5]
N (Experimental arm)	**550 (IPI-NIVO)**	**432 (PEM-AXI)**	**355 (PEM-LEN)**	**442 (AVE-AXI)**	**323 (CABO-NIVO)**
Median age, yr	62	62	64	62	62
Male sex, %	75	71	71.8	71.5	77.1
Nephrectomy, %	82	82.6	73.8	79.6	68.7
Sarcomatoid features, %	13.4	17.9	7.9		10.5
IMDC risk group, %					
• Favorable	23	31.9	31	21.3	22.9
• Intermediate	61	55.1	59.2	61.3	58.2
• Poor	17	13	9.3	16.3	18.9
ORR, %	39	60	71	52.5	54.8
CR, %	12	10	16	3.8	9.3
PD, %	18	11	5	12.4	6.2
Median FUP (months)	67.7	42.8	27	19.3	23.5
Subsequent anticancer therapy, %	55	58.4	68.2	20.8	31.8
OS					
Landmark 2 years	71	74	79	69	72
		Pooled 2y-OS for IO-TKI: 72%			
DoR					
Landmark 2 years	65	48.9	56	33	NR (56% 18m)
		Pooled 2y-DoR for IO-TKI: 51%			
PFS					
Landmark 2 years	37	40	50	31	38
		Pooled 2y-PFS for IO-TKI: 40%			

1. Motzer RJ, et al. *Annals of Oncology* (2021) 32 (suppl_5): S678-S724. 10.1016/annonc/annonc675; 2. Rini BI, et al. *J Clin Oncol* 39, 2021 (suppl 15; abstr 4500); 3. Motzer RJ, et al. *N Engl J Med*. 2021 Apr 8;384(14):1289-1300; 4. Choueiri TK, et al. *Ann Oncol.* 2020 Aug;31(8):1030-1039; 5. Motzer RJ, et al. *J Clin Oncol* 39, 2021 (suppl 6; abstr 308)

Courtesy of Andrea Necchi

Advanced ccRCC – 1st Line: LITESPARK-012

An Open-label, Randomized Phase 3 Study to Evaluate Efficacy and Safety of Pembrolizumab in Combination with Belzutifan and Lenvatinib, or MK-1308A in Combination with Lenvatinib, versus Pembrolizumab and Lenvatinib, as First-line Treatment in Participants with Advanced Clear Cell Renal Cell Carcinoma (ccRCC) (MK-6482-012)



IMDC, International mRCC Database Consortium; IV, intravenously; Q6W, every 6 weeks; Q12W, every 12 weeks; QD, once daily; R, randomization; ROW, rest of world.

[a]Documented disease progression, start of a new anticancer treatment, unacceptable toxicity, or withdrawal of the patient.

ClinicalTrials.gov Identifier NCT04736706

Choueiri T et al., Poster presented at at GU ASCO 2022

Advanced ccRCC – 1st Line: LITESPARK-012

Primary objectives:

- To compare the HIF triplet and CTLA4 triplet to the doublet (pembrolizumab + lenvatinib) with respect to PFS per RECIST 1.1 as assessed by BICR
- To compare the HIF triplet and CTLA4 triplet to the doublet (pembrolizumab + lenvatinib) with respect to OS

Primary endpoints

- **PFS by BICR**
- **OS**

Secondary endpoints

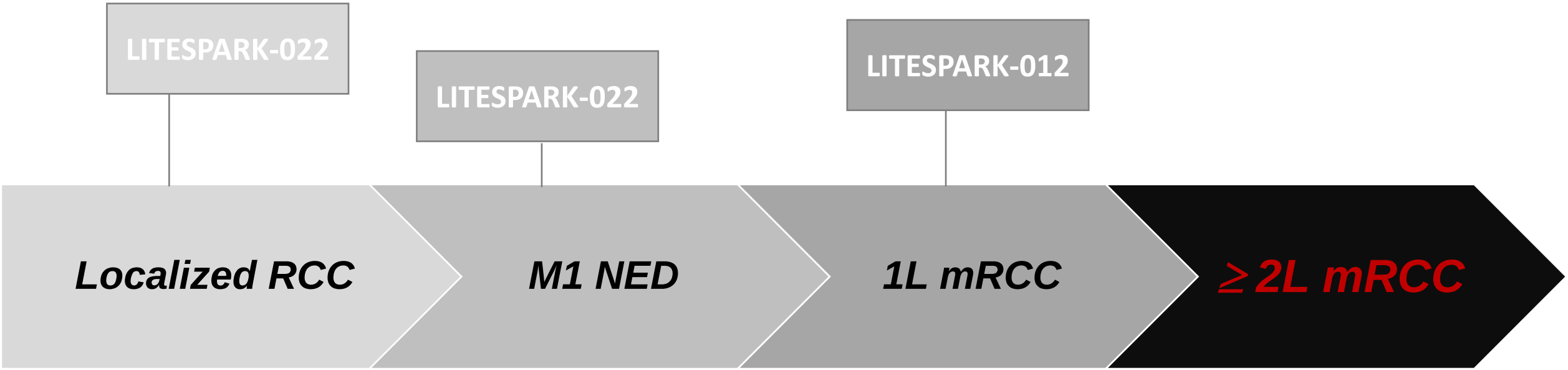
- ORR by BICR
- DOR by BICR
- Safety and tolerability

Exploratory endpoints

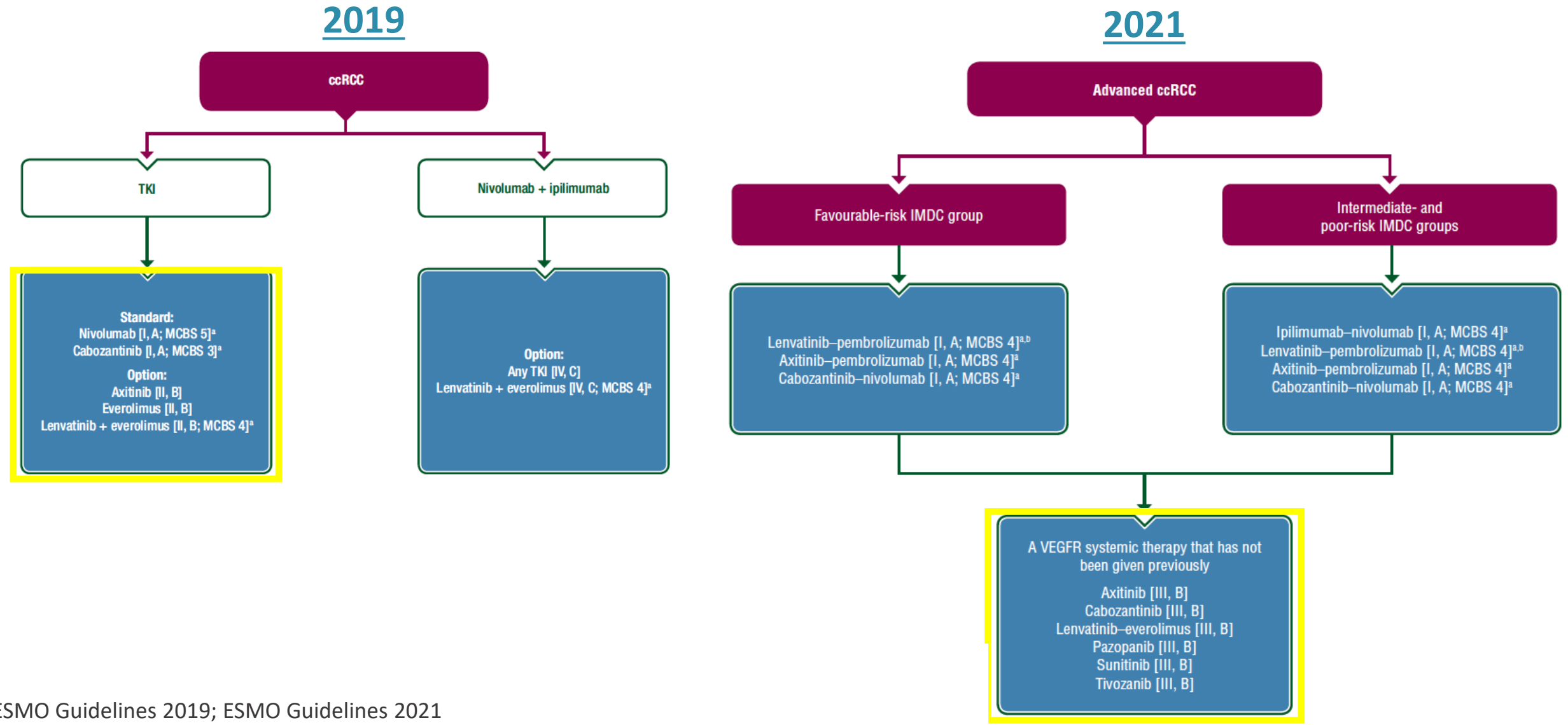
- PK belzutifan and MK-1308A
- PROs (FKSI-DRS, EORTC-QLQ-C30 and EuroQoL EQ-5D-5L)
- Biomarkers

ClinicalTrials.gov Identifier: NCT04736706

Clear cell renal cell carcinoma



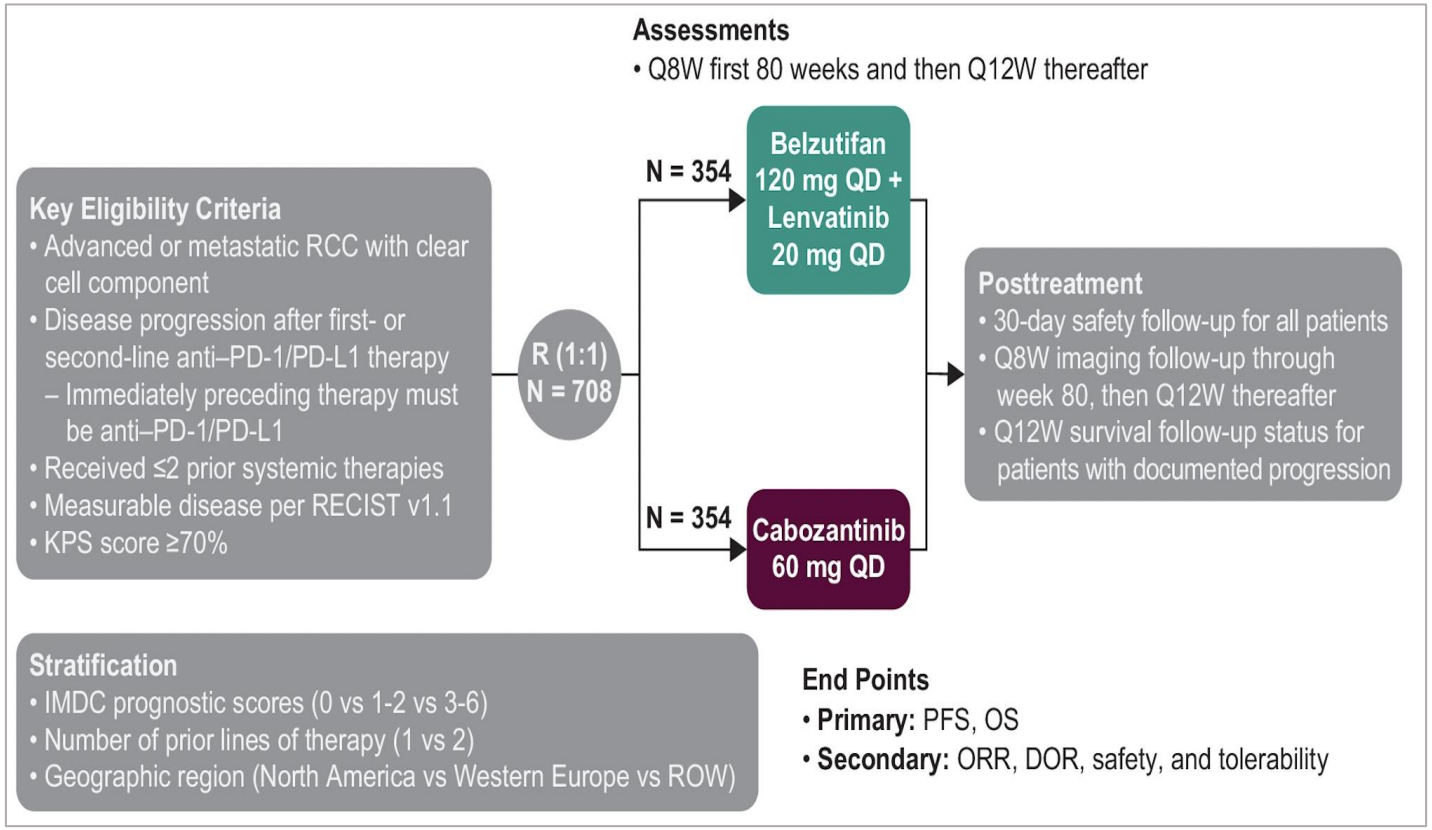
Advanced ccRCC – 2nd Line



ESMO Guidelines 2019; ESMO Guidelines 2021

Advanced ccRCC – 2/3 Line: LITESPARK-011

MK-6482-011: An Open-label, Randomized, Phase 3 Study of Belzutifan (MK-6482) In Combination with Lenvatinib (MK-7902) vs Cabozantinib for Treatment in Participants with Advanced Renal Cell Carcinoma Who Have Progressed After Prior Anti-PD-1/L1 Therapy



ClinicalTrials.gov Identifier: NCT04586231

Motzer RJ, et al. *J Clin Oncol*. 39, 2021 (suppl 6; abstr TPS372)

Advanced ccRCC – 2/3 Line: LITESPARK-011

Key inclusion criteria

1. Must have a histologically confirmed diagnosis of unresectable, locally advanced/metastatic RCC with clear cell component (with or without sarcomatoid features) ie, Stage IV RCC per AJCC (8th Edition).

2. **Has experienced disease progression on or after an anti-PD-1/L1 therapy as either first or second-line treatment for locally advanced/metastatic RCC or as adjuvant treatment with progression on or within 6 months of last dose.**
   Note: The anti-PD-1/L1 therapy may have been monotherapy or in combination with other agent(s) such as anti-CTLA4 or VEGF-targeted-TKI.
   The immediately preceding line of treatment has to have been an anti-PD-1/L1 therapy.

3. Has received **no more than 2 prior systemic regimens** for locally advanced or metastatic RCC

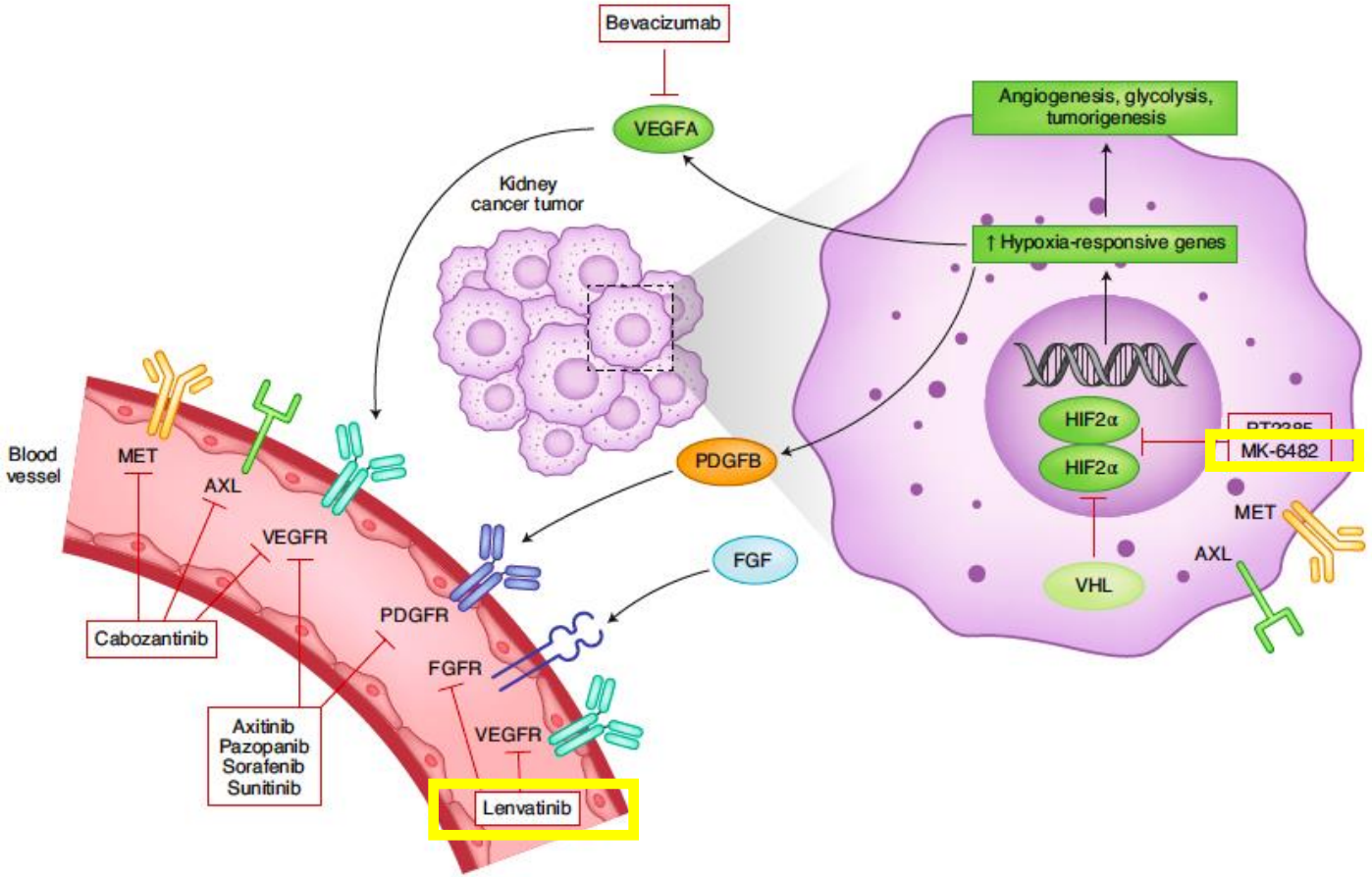
4. Has received **only 1 prior anti-PD-1/L1 therapy** for locally advanced or metastatic RCC

5. Has a KPS ≥70% assessed within 10 days prior to randomization

6. Adequately controlled BP

ClinicalTrials.gov Identifier: NCT04586231

Advanced ccRCC – 2/3 Line: LITESPARK-011



Lenvatinib + belzutifan

- **Lenvatinib** inhibits the kinase activities of VEGF receptors **VEGFR1**, **VEGFR2**, and **VEGFR3.**
- Lenvatinib inhibits other kinases implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including **FGFR1, 2, 3, and 4**; **PDGFRα**, **KIT**, and **RET**.
- As **HIF-2α** drives tumor cell expression of several oncogenes in ccRCC, the combination of **belzutifan + lenvatinib** could inhibit multiple oncogenic signaling pathways.
- The combination will provide enhanced VEGF inhibition through orthogonal mechanisms.

Choueiri T et al, Nat Medicine 2020; ClinicalTrials.gov Identifier: NCT04586231

Advanced ccRCC – 2/3 Line: LITESPARK-011

Hypothesis: Belzutifan (MK-6482) in combination with Lenvatinib is superior to Cabozantinib for therapeutic effect, including PFS, OS, and ORR.

Primary endpoints

- **Progression-free survival (PFS) by BICR**
- **Overall survival (OS)**

Secondary endpoints

- Objective Response Rate (ORR) by BICR
- Duration of Response (DOR) by BICR
- Adverse events
- Study intervention discontinuation due to AEs

Exploratory endpoints

PK belzutifan
PROs (FKSI-DRS, EORTC-QLQ-C30 and EuroQoL EQ-5D-5L)
Biomarkers

ClinicalTrials.gov Identifier: NCT04586231

Non-clear cell renal cell carcinoma

1L mPRCC

≥ 2L , non-ccRCC

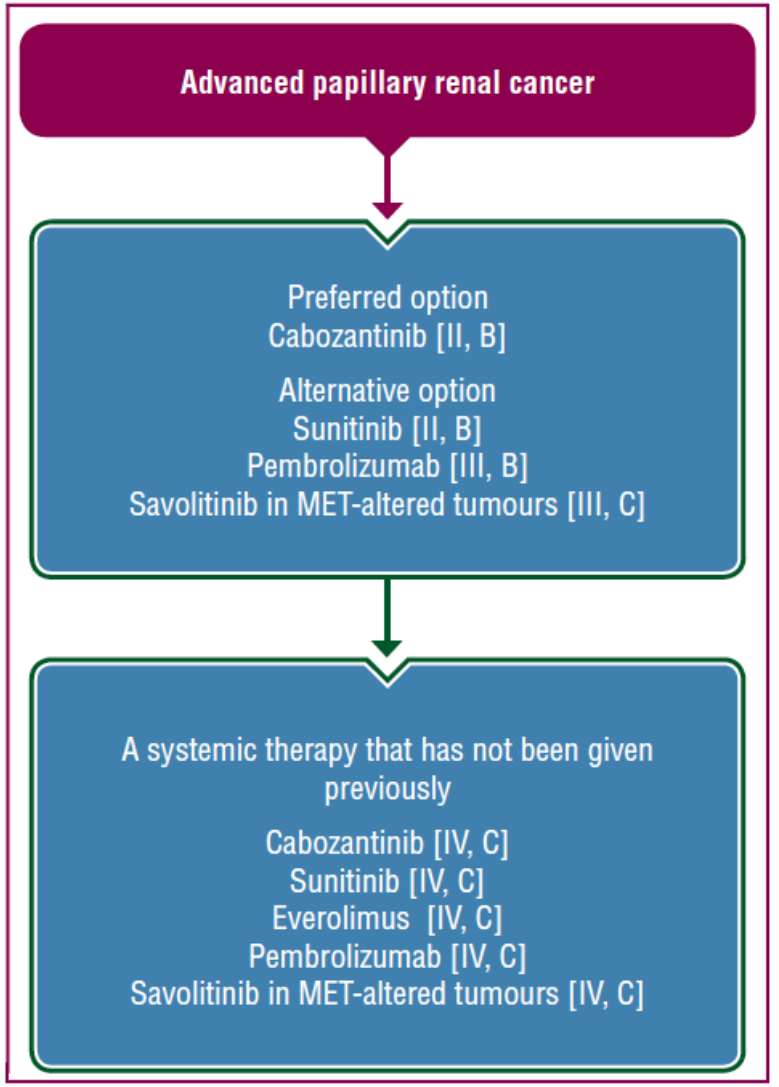
Non-clear cell renal cell carcinoma

1L mPRCC

≥ 2L , non-ccRCC

Advanced papillary renal cell carcinoma

- **Papillary renal cell carcinoma** (PRCC) is a form of non-clear cell RCC and the second most common subtype of RCC, accounting for 10–15% of cases
- Robust data remain elusive in this disease, mainly due to the challenges of conducting large, randomised trials in rare cancers.
- **Clinical trials are required in this disease.**
- **Many PRCC cases are MET-driven**, a result of genomic abnormalities resulting in dysregulation of the MET signaling pathway, making these abnormalities **a potential target for treatment**.
  - In a Phase II study in patients with advanced PRCC (NCT02127710), **approximately 40% of tumours** were found to be MET-driven

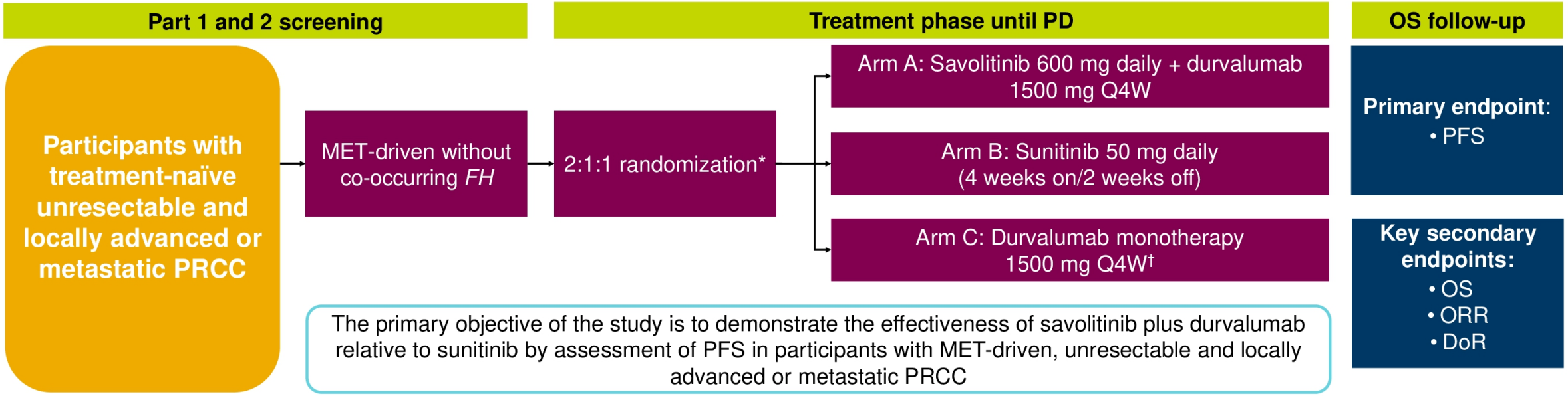


Choueiri TK, et al. J Clin Oncol 2017;35:2993; ESMO Guidelines 2021

Papillary renal cell carcinoma: the SAMETA trial

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) (SAMETA)

Figure 2. SAMETA trial design



*The first patient was enrolled on October 28, 2021

†Participants randomized to the durvalumab monotherapy arm will be allowed to cross-over to the savolitinib plus durvalumab arm at the time of BICR-confirmed PD per RECIST 1.1 without any intervening systemic anti-cancer therapy following discontinuation of durvalumab monotherapy. Cross-over will not be allowed in any other case

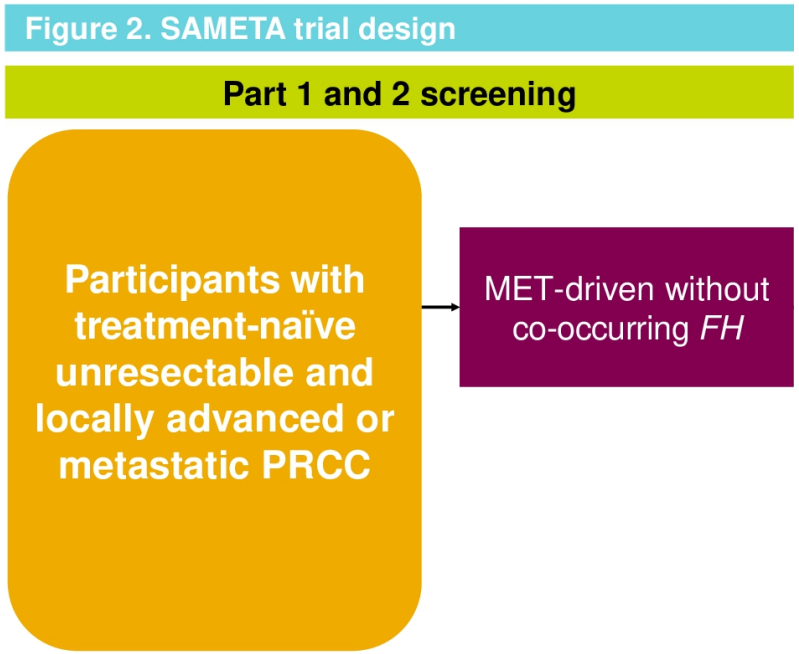
BICR, blinded independent central review; DoR, duration of response; *FH*, fumarate hydratase; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRCC, papillary renal cell carcinoma; RECIST 1.1, Response Evaluation Criteria in Solid Tumours; Q4W, every 4 weeks

ClinicalTrials.gov Identifier: NCT05043090

Choueiri T et al., Poster presented at at ASCO 2022

Papillary renal cell carcinoma: the SAMETA trial

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) (SAMETA)



–**Part 1 screening:** prospective testing of tumor specimens to determine MET-driven status without co-occurring *FH* mutations and PD-L1 biomarker status.
–**Part 2 screening:** involves determining whether the participant meets the rest of the eligibility criteria

MET-driven PRCC: detection of chromosome 7 gain, MET amplification, MET kinase domain variations, and / or *HGF* amplification (in the absence of co-occurring *FH* mutations) by central NGS testing

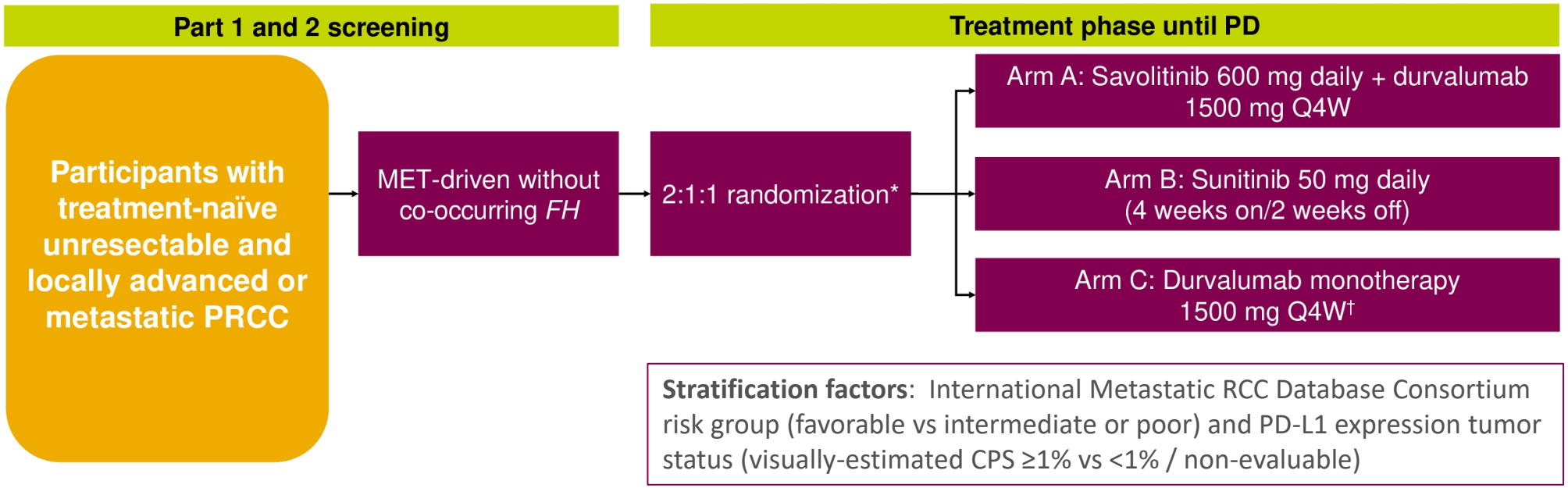
ClinicalTrials.gov Identifier: NCT05043090

Choueiri T et al., Poster presented at at ASCO 2022

Papillary renal cell carcinoma: the SAMETA trial

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) (SAMETA)

Figure 2. SAMETA trial design



ClinicalTrials.gov Identifier: NCT05043090

Choueiri T et al., Poster presented at at ASCO 2022

Papillary renal cell carcinoma: the SAMETA trial

Savolitinib

Savolitinib is an oral, potent, and highly selective MET TKI.

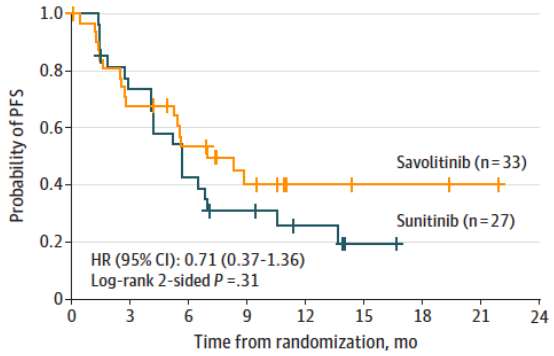
- In the Phase III **SAVOIR study** (NCT03091192), savolitinib demonstrated encouraging antitumor activity compared with standard-of-care sunitinib in patients with MET-driven PRCC: PFS, OS, and ORR were all numerically greater with savolitinib vs sunitinib
- Sample size and follow-up were limited in SAVOIR due to premature termination of the study

JAMA Oncology | Original Investigation

Efficacy of Savolitinib vs Sunitinib in Patients With *MET*-Driven Papillary Renal Cell Carcinoma

The SAVOIR Phase 3 Randomized Clinical Trial

A Blinded independent central review-assessed PFS

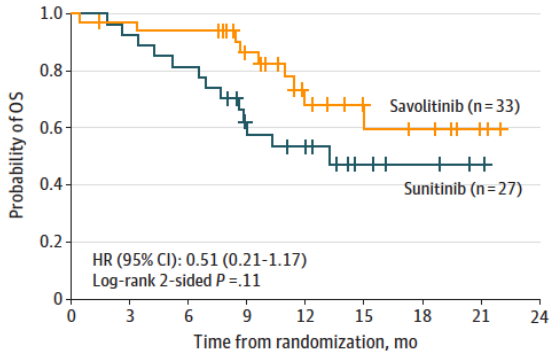


No. at risk

Savolitinib	33	21	15	8	4	3	3	1	0
Sunitinib	27	19	11	7	4	1	0	0	0

	Number Randomized	Number of Events	Median PFS in months (95% CI)
Savolitinib	33	17	7.0 (2.8-NC)
Sunitinib	27	20	5.6 (4.1-6.9)

B Blinded independent central review-assessed OS



No. at risk

Savolitinib	33	31	30	22	13	7	6	2	0
Sunitinib	27	25	22	14	10	5	3	1	0

	Number Randomized	Number of Events	Median OS in months (95% CI)
Savolitinib	33	9	NC (11.9-NC)
Sunitinib	27	13	13.2 (7.6-NC)

Choueiri T et al, Jama Oncol 2020

Papillary renal cell carcinoma: the SAMETA trial

Savolitinib + Durvalumab

- The MET pathway may also play a role in immunomodulation.
- Non-clinical and clinical data suggest **a possible synergistic antitumor effect** of MET inhibitors with an immune checkpoint inhibitor, such as durvalumab

- The Phase I / II **CALYPSO study** (NCT02819596) investigating savolitinib plus durvalumab, showed a notable efficacy signal in patients with MET-driven PRCC
- ORR was 57%, median PFS was 10.5 months (95% CI 2.9, 15.7) and median OS was 27.4 months (95% CI 7.3, not reached)

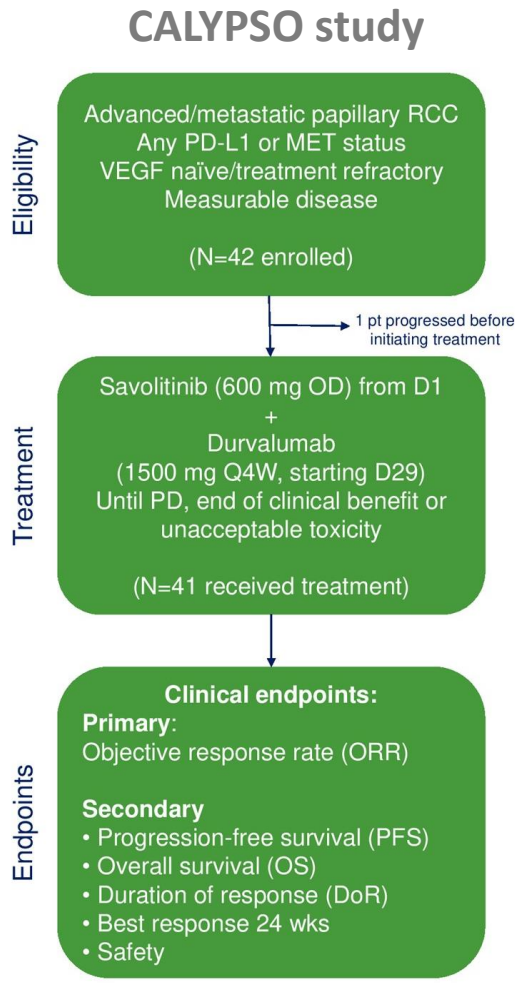


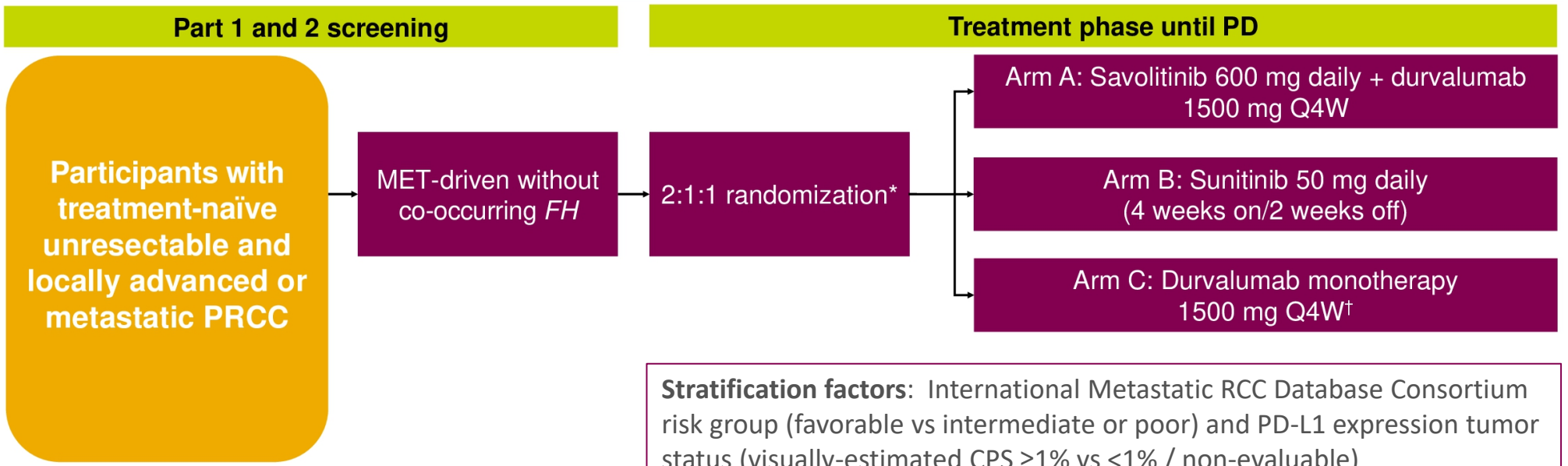
Fig. 1: Study Design

Suarez Rodriguez C, et al. *J Clin Oncol* 2021;39(Suppl_15):4511; Choueiri T et al, Jama Oncol 2020

Papillary renal cell carcinoma: the SAMETA trial

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) (SAMETA)

Figure 2. SAMETA trial design



Arm C: **cross-over** to Arm A at the time of BICR-confirmed PD per RECIST 1.1 allowed

ClinicalTrials.gov Identifier: NCT05043090

Choueiri T et al., Poster presented at at ASCO 2022

Papillary renal cell carcinoma: the SAMETA trial

The primary objective of the study is to demonstrate the **effectiveness of savolitinib plus durvalumab relative to sunitinib** by assessment of PFS in participants with MET-driven, unresectable and locally advanced or metastatic PRCC

Primary endpoint

- **PFS (durvalumab + savolitinib vs. sunitinib)**

Secondary endpoints

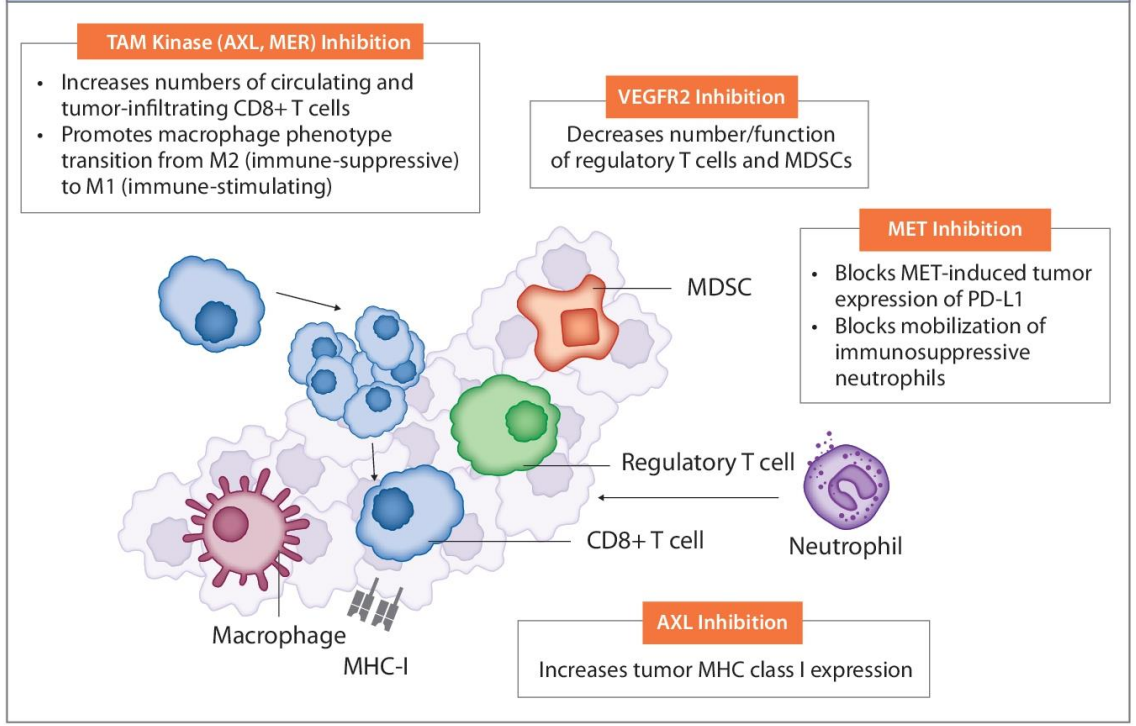
- OS, ORR, DoR, DCR at 24 and 48 weeks, PFS2 (durvalumab + savolitinib vs. sunitinib)
- PFS, ORR, DoR (durvalumab + savolitinib vs. durvalumab)
- HRQoL (FKSI-19)
- PK of savolitinib and durvalumab
- Safety

Non-clear cell renal cell carcinoma

Pretreated Advanced RCC: STELLAR-01

A Dose-Escalation and Expansion Study of the Safety and Pharmacokinetics of XL092 as Single-Agent and Combination Therapy in Subjects with Inoperable Locally Advanced or Metastatic Solid Tumors

Figure 1. XL092 Targets Pathways Associated With Tumor Immunosuppression



- **XL092** is a **novel multi-targeted inhibitor of receptor tyrosine kinases** including MET, VEGFR2, and the TAM kinases AXL and MER, which play roles in tumor growth and metastasis, angiogenesis, and immune suppression of the tumor microenvironment.
- XL092 has a **relatively short half-life** (~21 hours) to support convenient daily dosing and help manage tolerability.

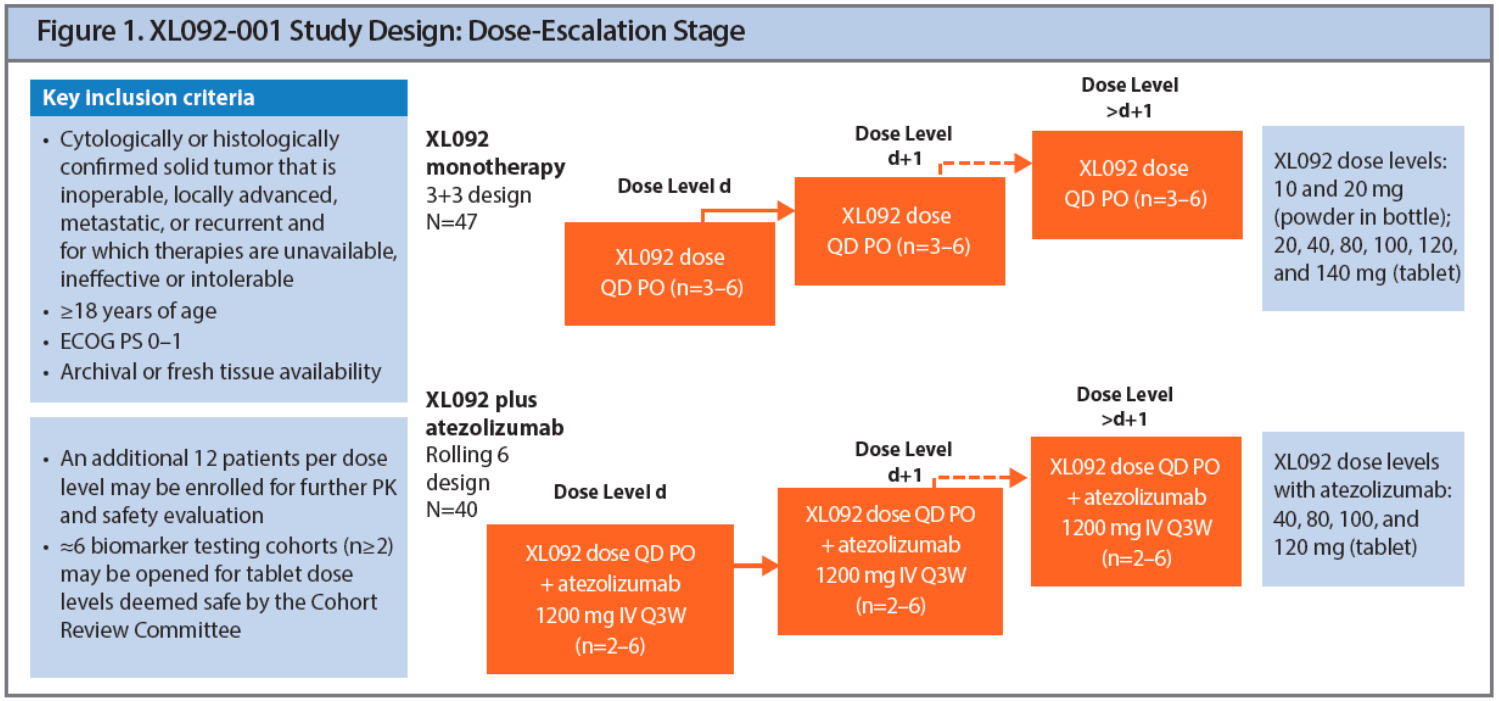
Choueiri T et al., Poster presented at at ASCO 2022

ClinicalTrials.gov Identifier: NCT03845166

Pretreated Advanced RCC: STELLAR-01

A Dose-Escalation and Expansion Study of the Safety and Pharmacokinetics of XL092 as Single-Agent and Combination Therapy in Subjects with Inoperable Locally Advanced or Metastatic Solid Tumors

Figure 1. XL092-001 Study Design: Dose-Escalation Stage



- XL092 demonstrated a manageable safety profile with no unexpected Aes relative to current receptor TKIs.
- The recommended dose for XL092 was 100 mg, for both monotherapy and in combination with atezolizumab
- Expansion cohorts are ongoing in a number of tumor types, including clear cell and non-clear cell RCC, HR+BC, mCRPC, and CRC

Manish R. Sharma et al, poster presented at ESMO 2022

ClinicalTrials.gov Identifier: NCT03845166

Pretreated Advanced RCC: STELLAR-01

A Dose-Escalation and Expansion Study of the Safety and Pharmacokinetics of XL092 as Single-Agent and Combination Therapy in Subjects with Inoperable Locally Advanced or Metastatic Solid Tumors

EXPANSION COHORTS XL092

ccRCC (Cohort A) N≤32	nccRCC (Cohort B) N≤32
HR+ BC (Cohort C) N≤43	mCRPC (Cohort D) N≤39

EXPANSION COHORTS XL092 + Atezolizumab

nccRCC (Cohort E) N≤21	HR+BC (Cohort F) N≤39
mCRPC (Cohort G) N≤26	CRC (Cohort H) N≤104

Primary endpoints
- ORR as assessed by the Investigator per RECIST 1.1
- PFS at 6 months per RECIST 1.1 as assessed by the Investigator

Secondary endpoints
- Severity of nonserious AEs and SAEs, including irAEs, and AESIs

Exploratory endpoints
- DOR as assessed by the Investigator per RECIST 1.1
- PFS as assessed by the Investigator per RECIST 1.1
- ORR, DOR, and PFS by BIRC per RECIST 1.1 for selected cohorts
- OS

ClinicalTrials.gov Identifier: NCT03845166

Pretreated Advanced RCC: STELLAR-01

A Dose-Escalation and Expansion Study of the Safety and Pharmacokinetics of XL092 as Single-Agent and Combination Therapy in Subjects with Inoperable Locally Advanced or Metastatic Solid Tumors

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HR+ BC (Cohort C) N≤43	mCRPC (Cohort D) N≤39

EXPANSION COHORTS XL092 + Atezolizumab

nccRCC (Cohort E) N≤21	HR+BC (Cohort F) N≤39
mCRPC (Cohort G) N≤26	CRC (Cohort H) N≤104

Cohort A (ccRCC):

- advanced RCC with clear cell histology (including those with a sarcomatoid component)
- radiographic PD following treatment with at least 1 prior systemic anticancer regimen for inoperable locally advanced or metastatic disease.
- *Allowed are a maximum of 3 prior systemic anticancer regimens for inoperable locally advanced or metastatic RCC.*

ClinicalTrials.gov Identifier: NCT03845166

Pretreated Advanced RCC: STELLAR-01

A Dose-Escalation and Expansion Study of the Safety and Pharmacokinetics of XL092 as Single-Agent and Combination Therapy in Subjects with Inoperable Locally Advanced or Metastatic Solid Tumors

EXPANSION COHORTS XL092

ccRCC (Cohort A) N≤32	nccRCC (Cohort B) N≤32
HR+ BC (Cohort C) N≤43	mCRPC (Cohort D) N≤39

EXPANSION COHORTS XL092 + Atezolizumab

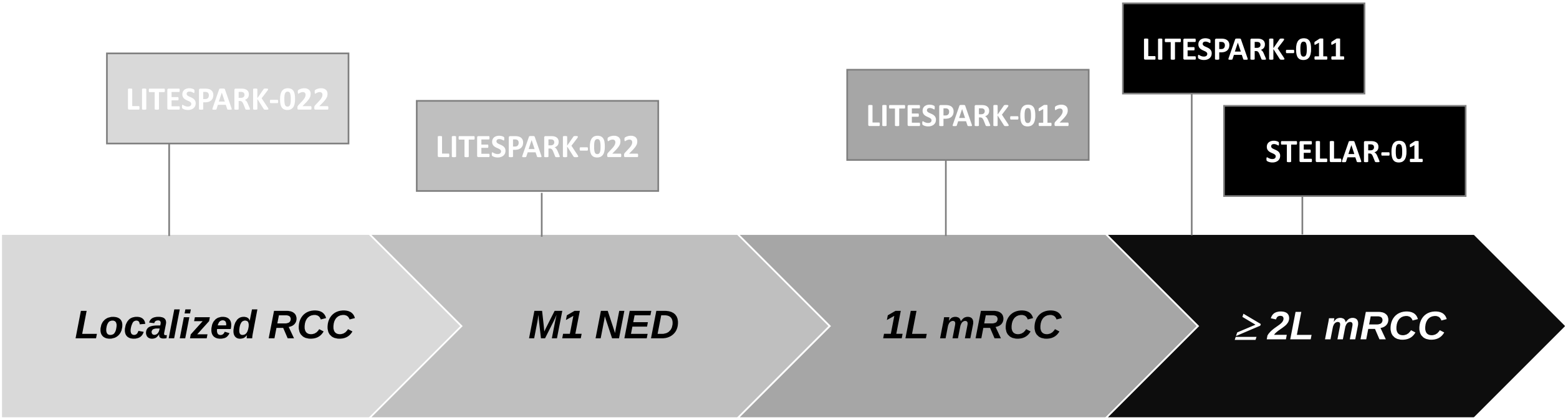
nccRCC (Cohort E) N≤21	HR+BC (Cohort F) N≤39
mCRPC (Cohort G) N≤26	CRC (Cohort H) N≤104

Cohorts B and E (nccRCC):

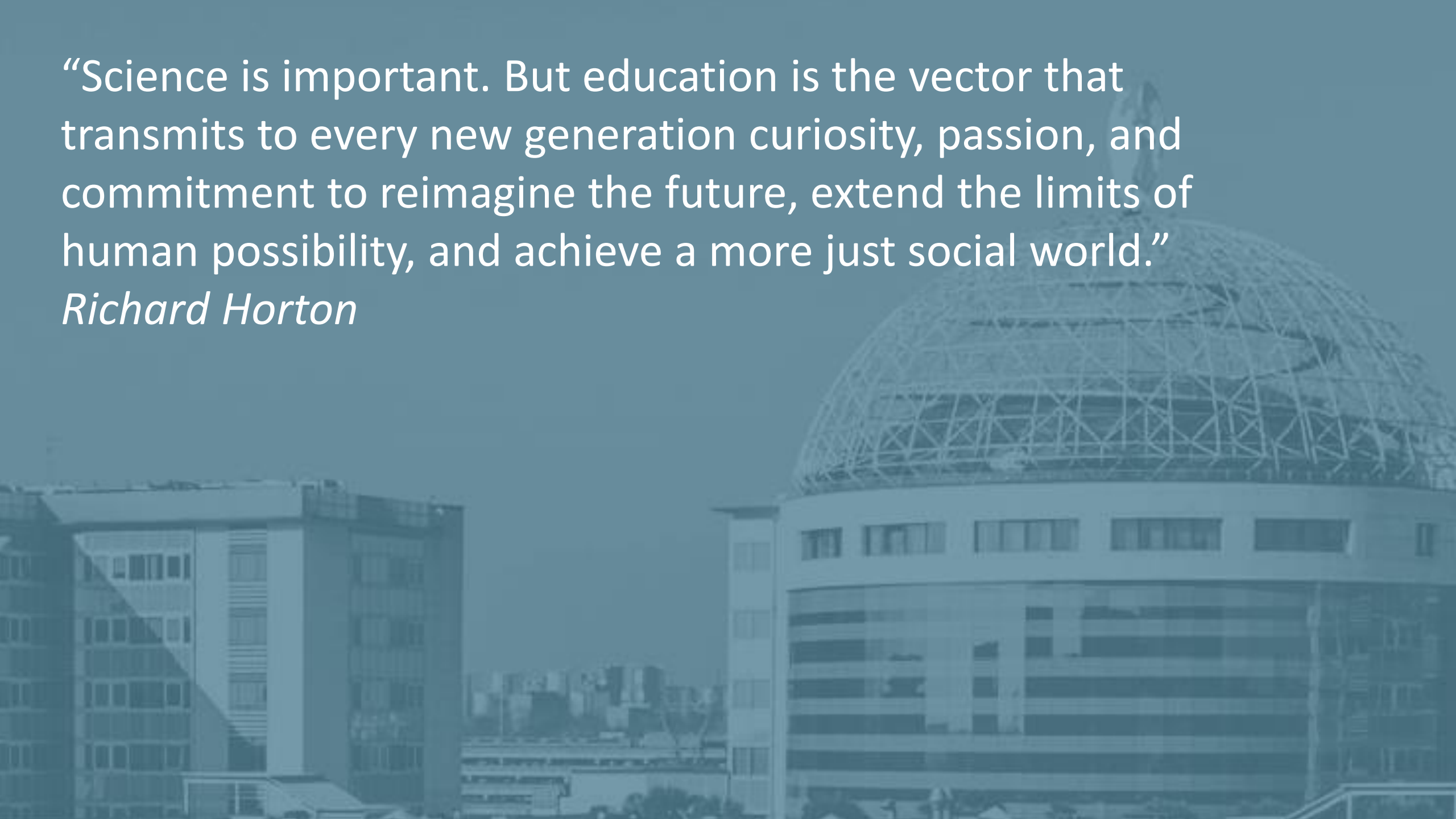
- previously treated advanced RCC with non-clear cell histology
- radiographic PD following treatment with at least one prior systemic anticancer regimen for inoperable locally advanced or metastatic disease.
- *Allowed are a maximum of 3 prior systemic anticancer regimens for inoperable locally advanced or metastatic nccRCC..*
- *For Cohort E, prior immune checkpoint inhibitor (ICI) therapy is not allowed.*

ClinicalTrials.gov Identifier: NCT03845166

Clear cell renal cell carcinoma



Non-clear cell renal cell carcinoma



“Science is important. But education is the vector that transmits to every new generation curiosity, passion, and commitment to reimagine the future, extend the limits of human possibility, and achieve a more just social world.”
Richard Horton