HIF2a inhibitors RCC

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MaTOS
March 2025

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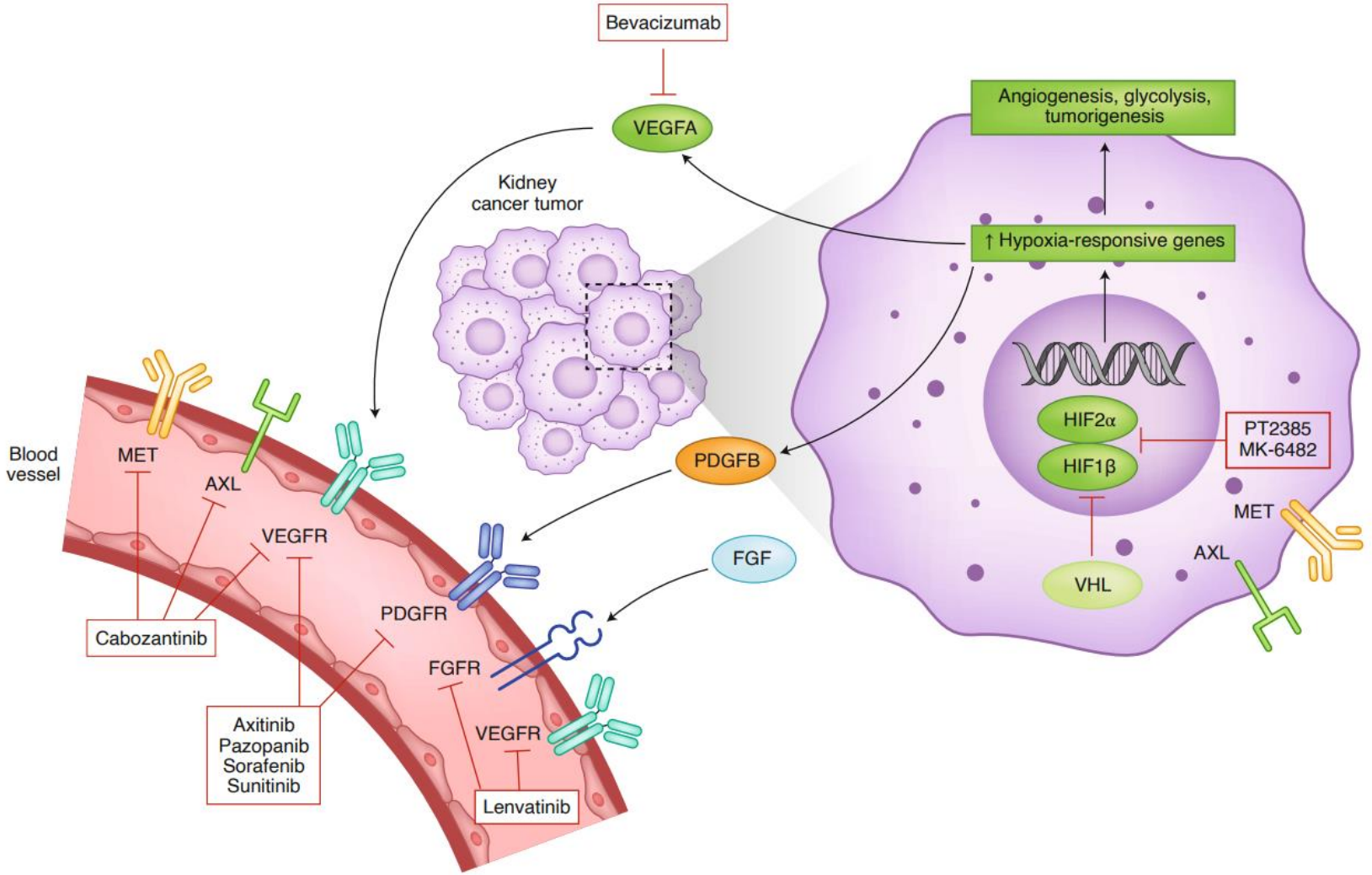

Multiple HIF-2a Inhibitors:

Belzutifan
NKT2152
Casdatifan (AB521)

Choueiri T: Nature Medicine 2020

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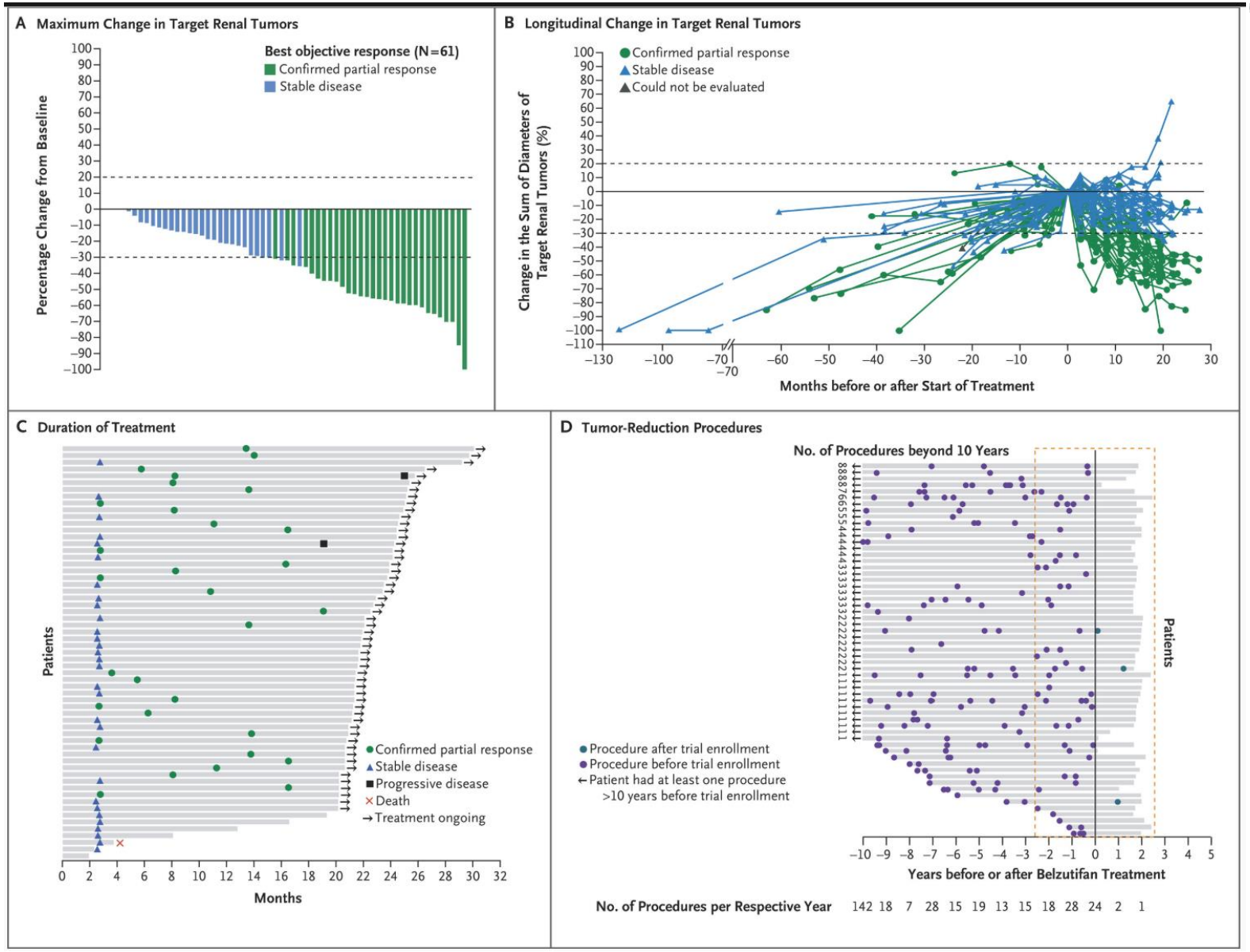
Belzutifan VHL Germline:

	RCC N = 61
ORR, % (95% CI)	**64 (50.6-75.8)**
Best response n (%)	
CR	4 (7)
PR	35 (57)
SD	21 (34)
PD	0
NE[a]	1 (2)



Jonasch; NEJM 2021

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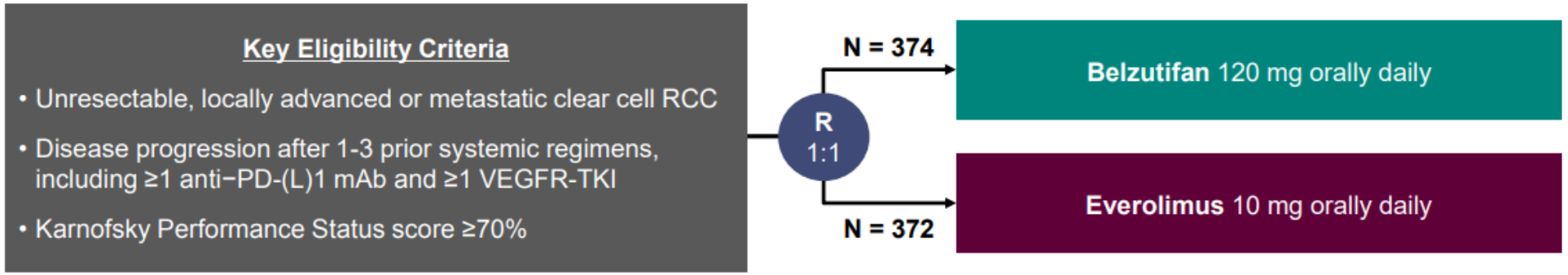
LITESPARK 005



Stratification Factors
- IMDC prognostic score[a]: 0 vs 1-2 vs 3-6
- Prior VEGF/VEGFR-targeted therapies: 1 vs 2-3

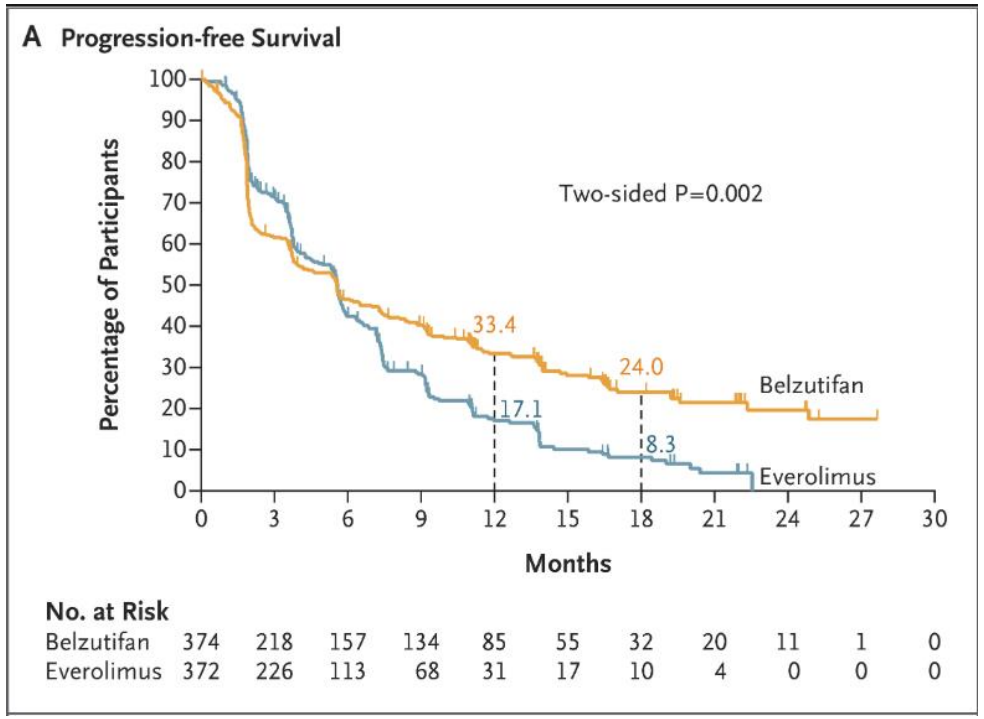
Dual Primary Endpoints:
- PFS per RECIST 1.1 by BICR
- OS

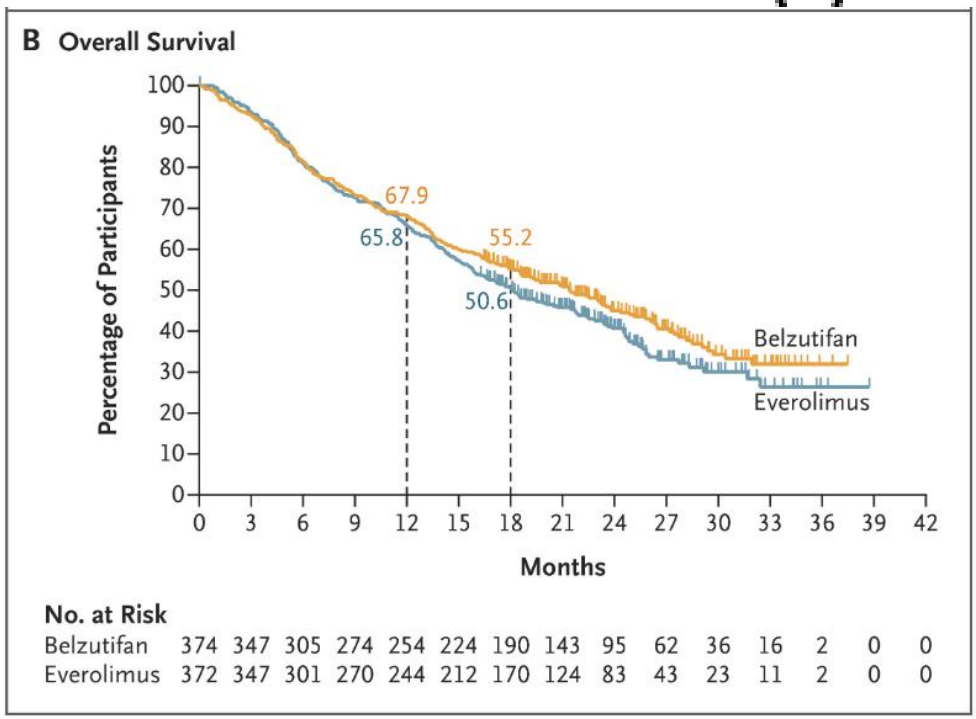
Key Secondary Endpoint:
- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:
- DOR per RECIST 1.1 by BICR
- Safety
- Time to deterioration in FKSI-DRS and EORTC QLQ-C30 GHS/QoL

Albiges; ESMO 2023

LITESPARK 005





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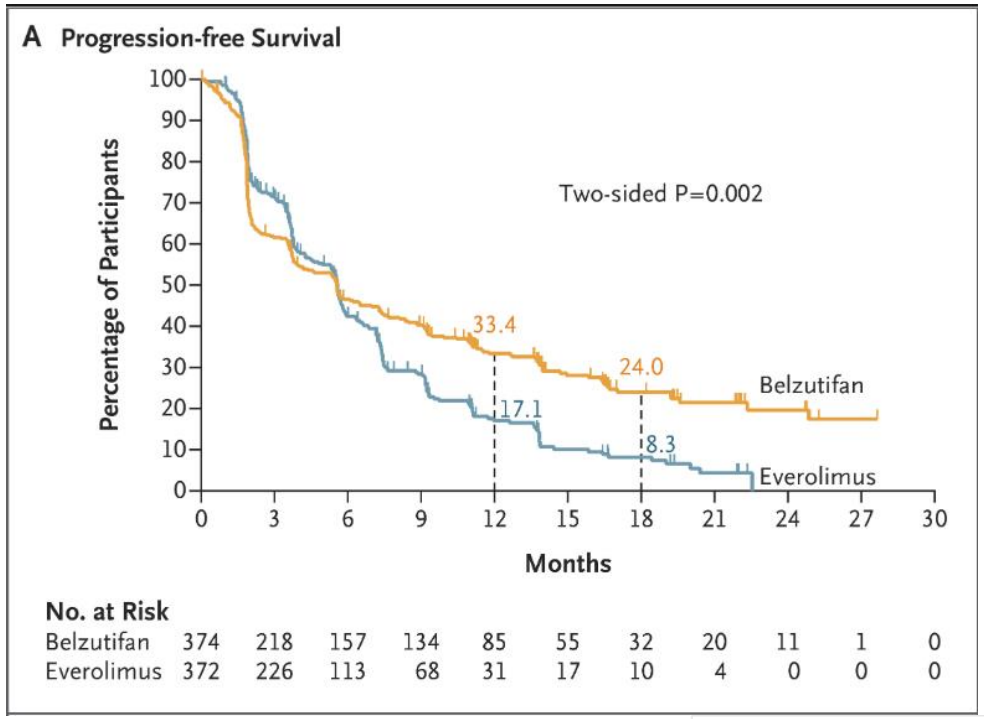

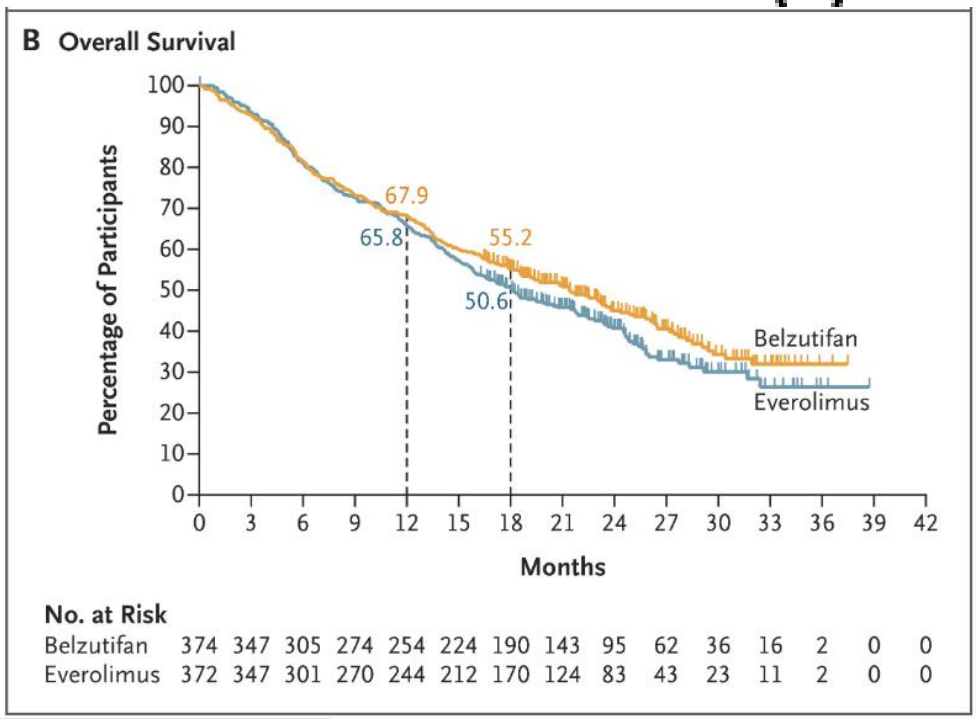

Response	First Interim Analysis	
	Belzutifan (N=374)	Everolimus (N=372)
Objective response — % (95% CI)	21.9 (17.8–26.5)	3.5 (1.9–5.9)
Confirmed best overall response — no. (%)		
Complete response	10 (2.7)	0
Partial response	72 (19.3)	13 (3.5)
Stable disease‡	147 (39.3)	245 (65.9)
Progressive disease	126 (33.7)	80 (21.5)

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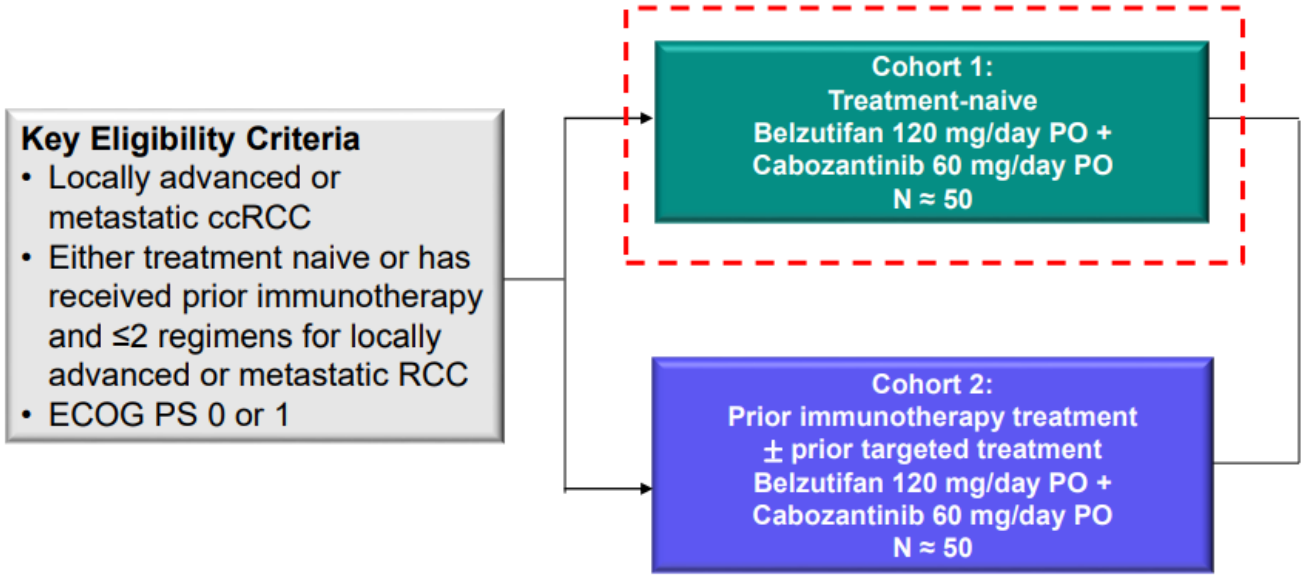
LITESPARK 003

Study Design of LITESPARK-003 (NCT03634540)



Tumor Assessments

- Week 9, then Q8W through month 12 and Q12W thereafter

End Points

- Primary: ORR per RECIST v1.1 by investigator
- Secondary: PFS, DOR, and TTR per RECIST v1.1 by investigator, OS, safety/tolerability

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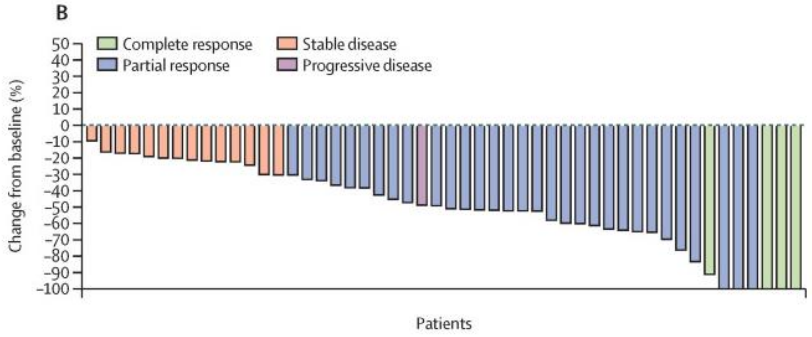
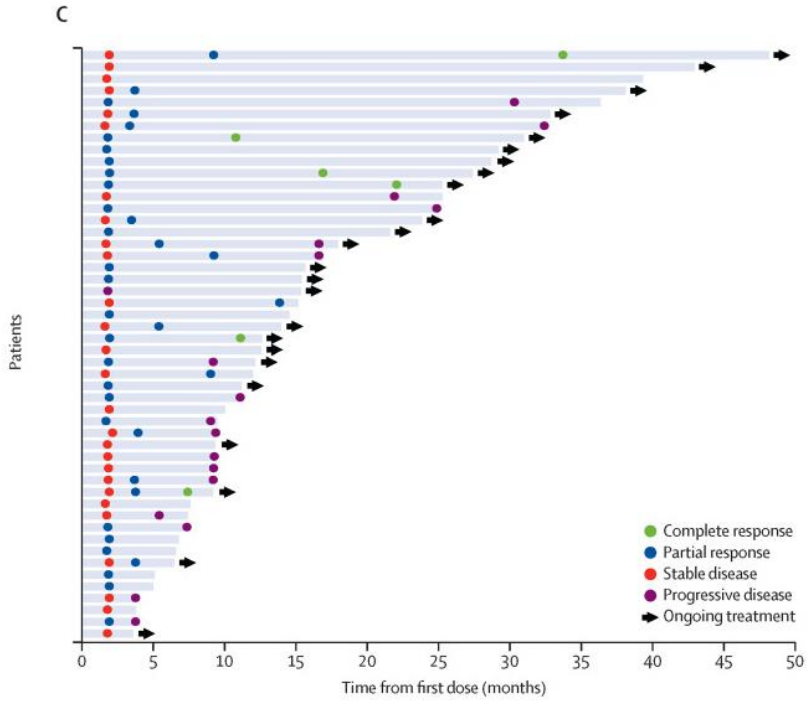
COHORT 1

Table 2. Best overall response per Response Evaluation Criteria in Solid Tumors version 1.1 by investigator

	Overall (n=50)	International Metastatic Renal Cell Carcinoma Database Consortium risk group*	
		Favourable (n=28)	Intermediate or poor (n=22)
Proportion of patients with confirmed objective response	35 (70%; 55–82)	22 (79%; 59–92)	13 (59%; 36–79)
Proportion of patients with disease control*	49 (98%; 89–100)	28 (100%; 88–100)	21 (96%; 77–100)
Best overall response			
Complete response	4 (8%)	3 (11%)	1 (5%)
Partial response	31 (62%)	19 (68%)	12 (55%)
Stable disease	14 (28%)	6 (21%)	8 (36%)
Progressive disease	1 (2%)	0	1 (5%)





Choueiri; Lancet 2025

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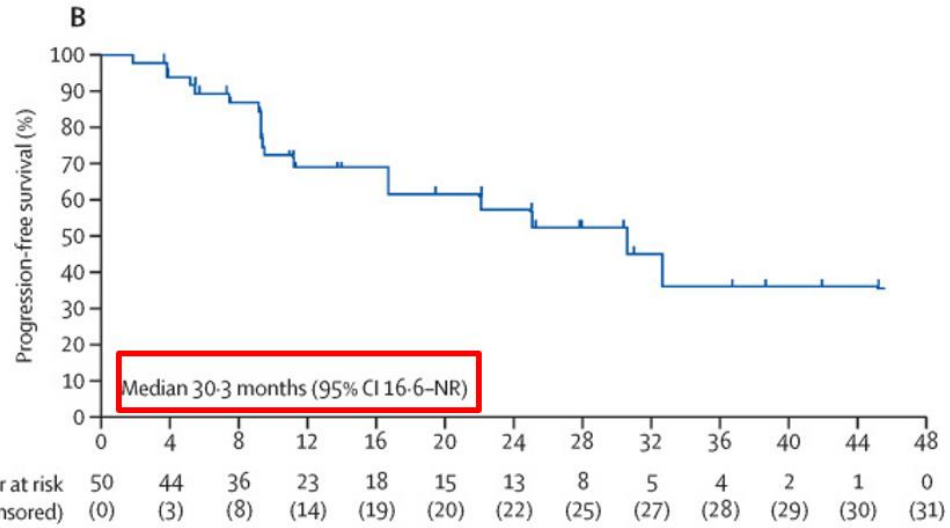

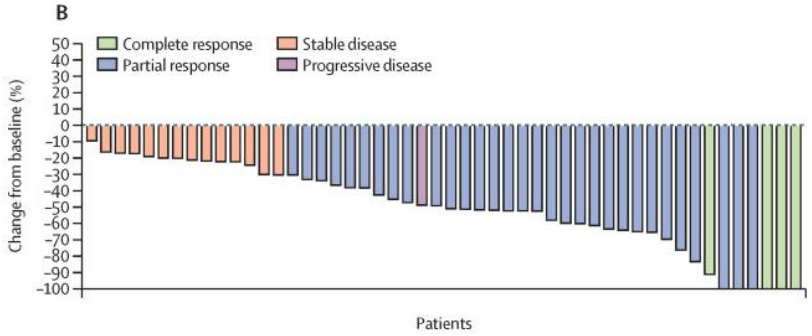

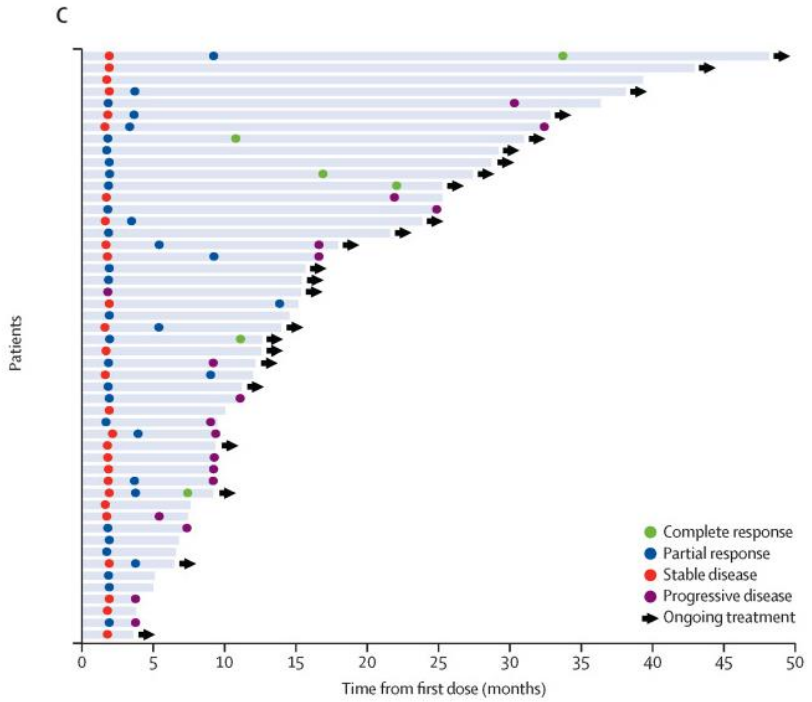

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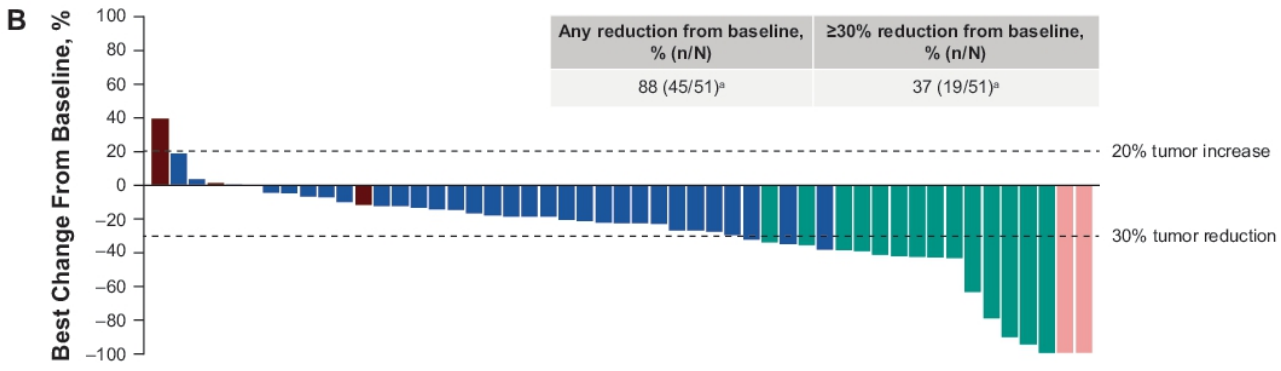
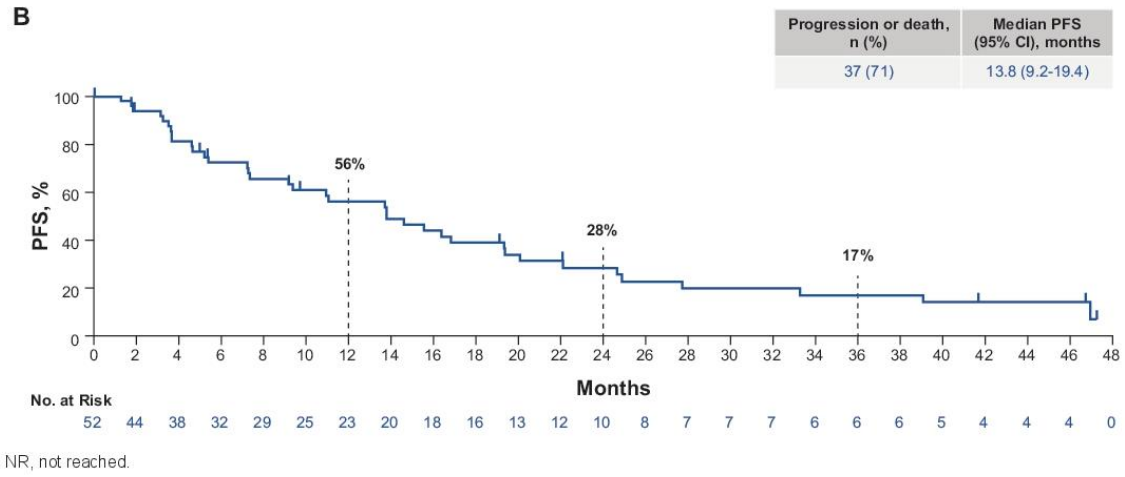
COHORT 2

	Cohort 2 n = 52
ORR[a] (95% CI), %	31 (19-45)
DCR[b] (95% CI), %	92 (81-98)
Best response, n (%)	
CR	2 (4)
PR	14 (27)
SD	32 (62)
PD	3 (6)
Not available[c]	1 (2)
TTR, median (range), months	3.2 (1.5-16.6)
DOR,[d] median (range), months	30.4 (4.2+ to 45.6)
Participants with ≥24 months response duration,[d] % (95% CI)	52 (25-74)





NR, not reached.

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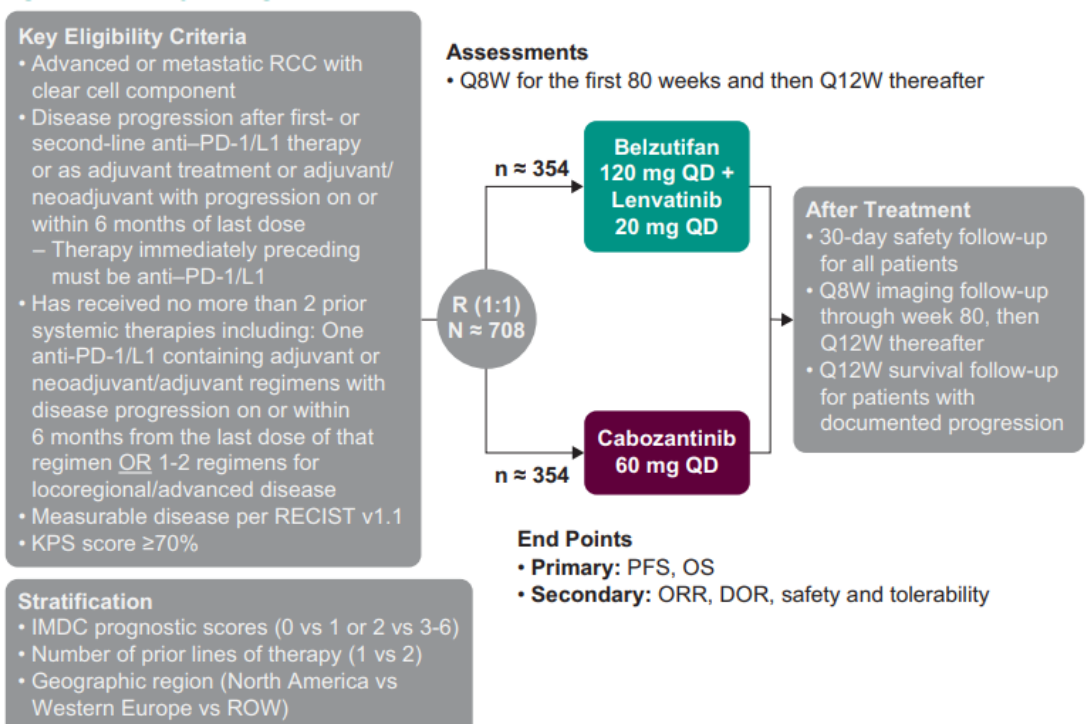
LITESPARK-011



Heng D; KCRS 2022

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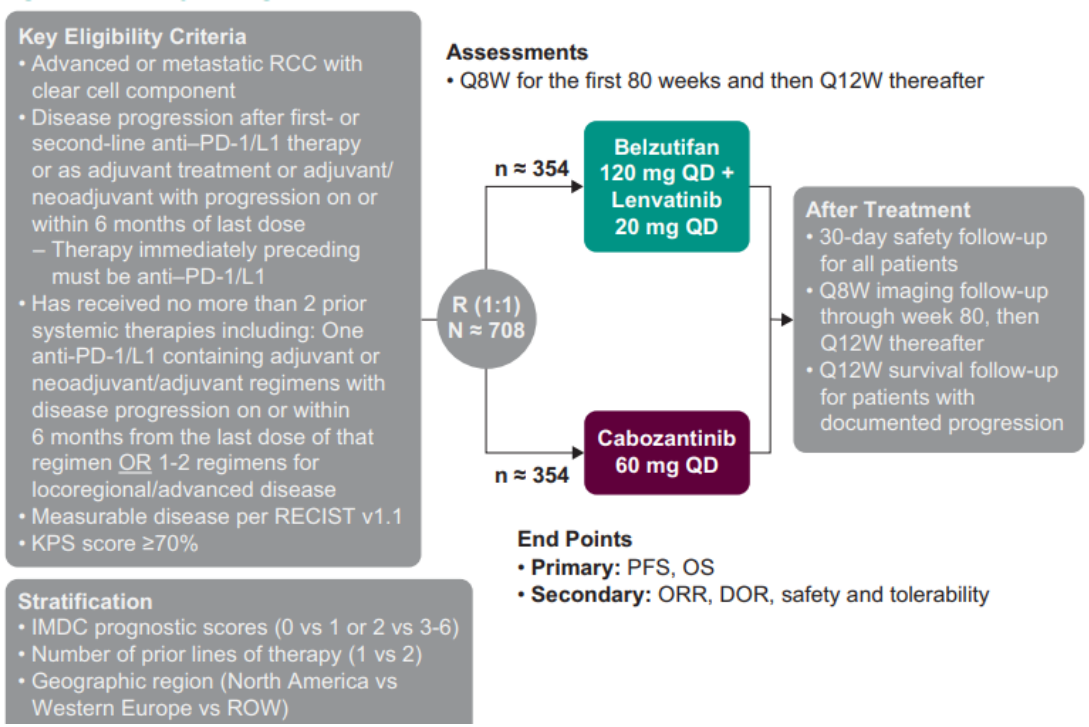

Heng D; KCRS 2022

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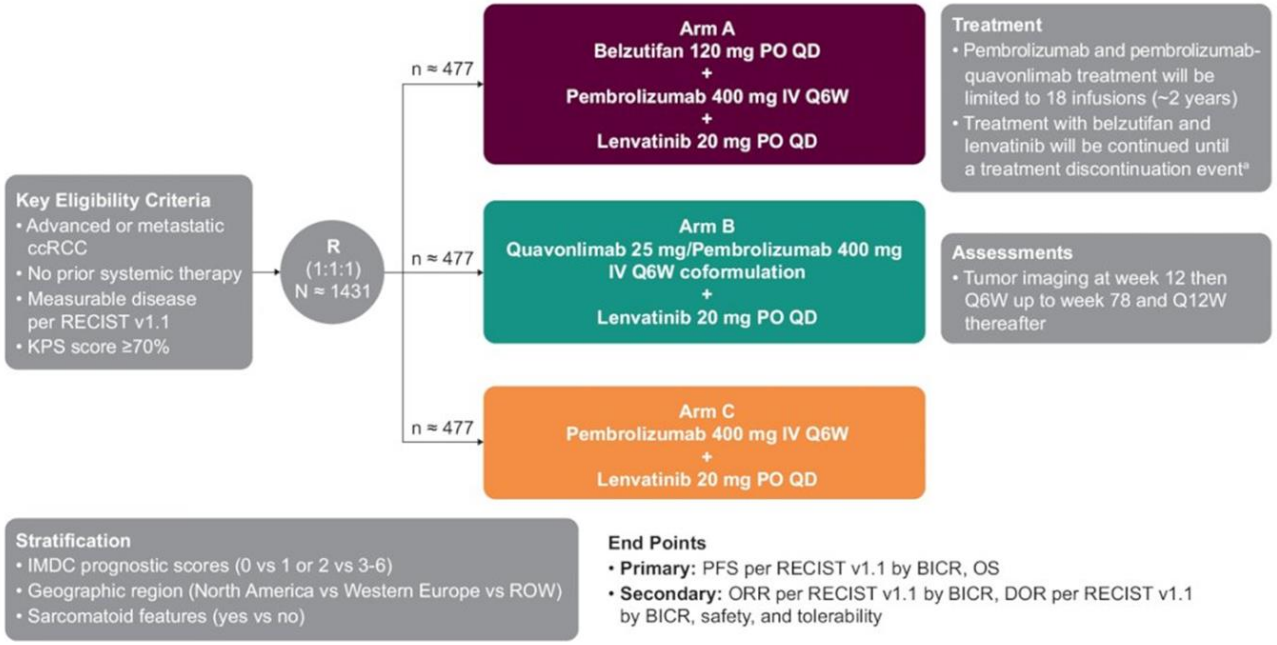

Rini; ESMO 2021

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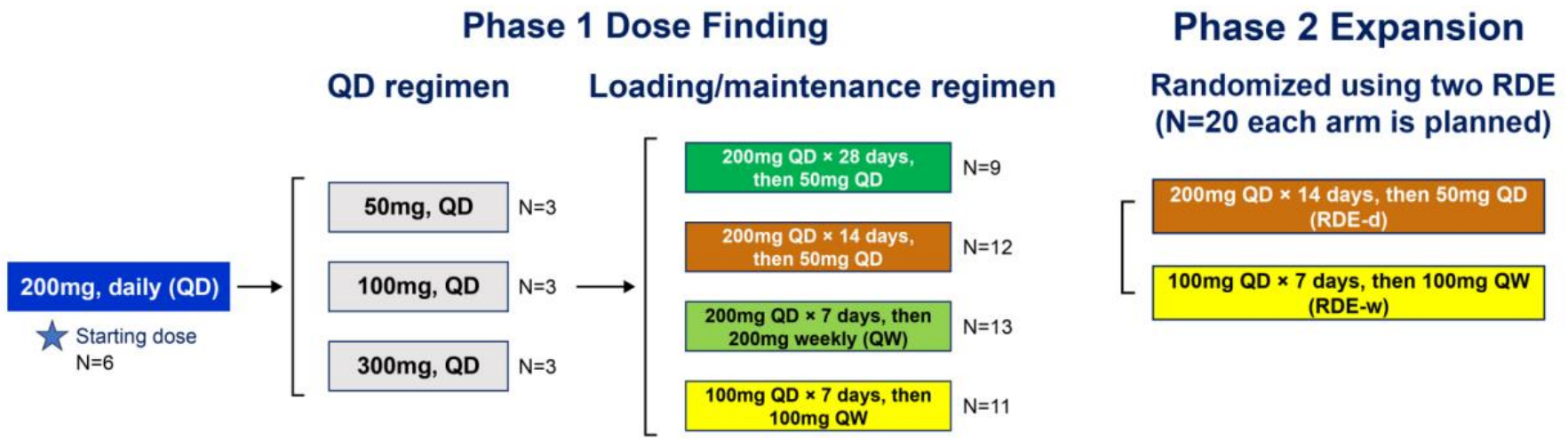
NKT2152-101 Phase 1/2 Design

Four daily doses and four loading/maintenance dosing regimens were evaluated



Initial dose escalation with daily dosing. Significant accumulation was observed.

To rapidly achieve therapeutic exposures and then maintain them, loading/maintenance regimens were evaluated.

Randomized dose evaluation is ongoing

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Eric Jonasch, MD

NCI Designated Comprehensive Cancer Center

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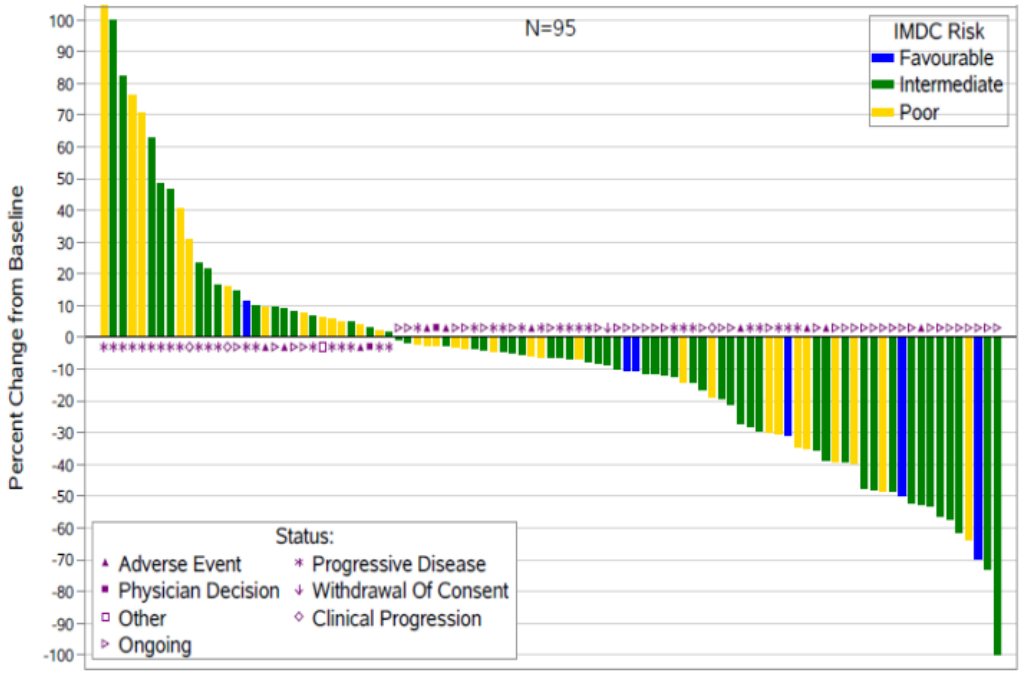
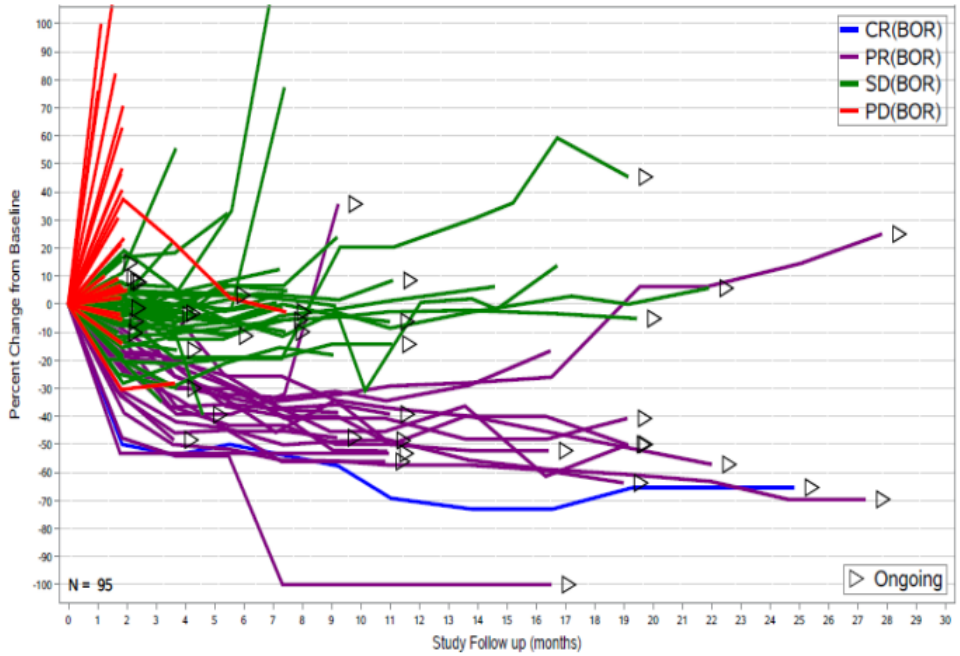
	All Patients (N=100)	Part 1 Patients (N=57)
Best Overall Response, n (%)		
CR	1 (1.00)	1 (1.75)
PR	19 (19.0)	14 (24.6)
SD	52 (52.0)	28 (49.1)
PD	28 (28.0)	14 (24.6)

Median TTR (range), months	3.7 (1.6-9.1)
Median DOR (95% CI)	NE (8.31, NE)
DCR (95% CI)	60% (50%, 70%)

Median PFS was 7.4





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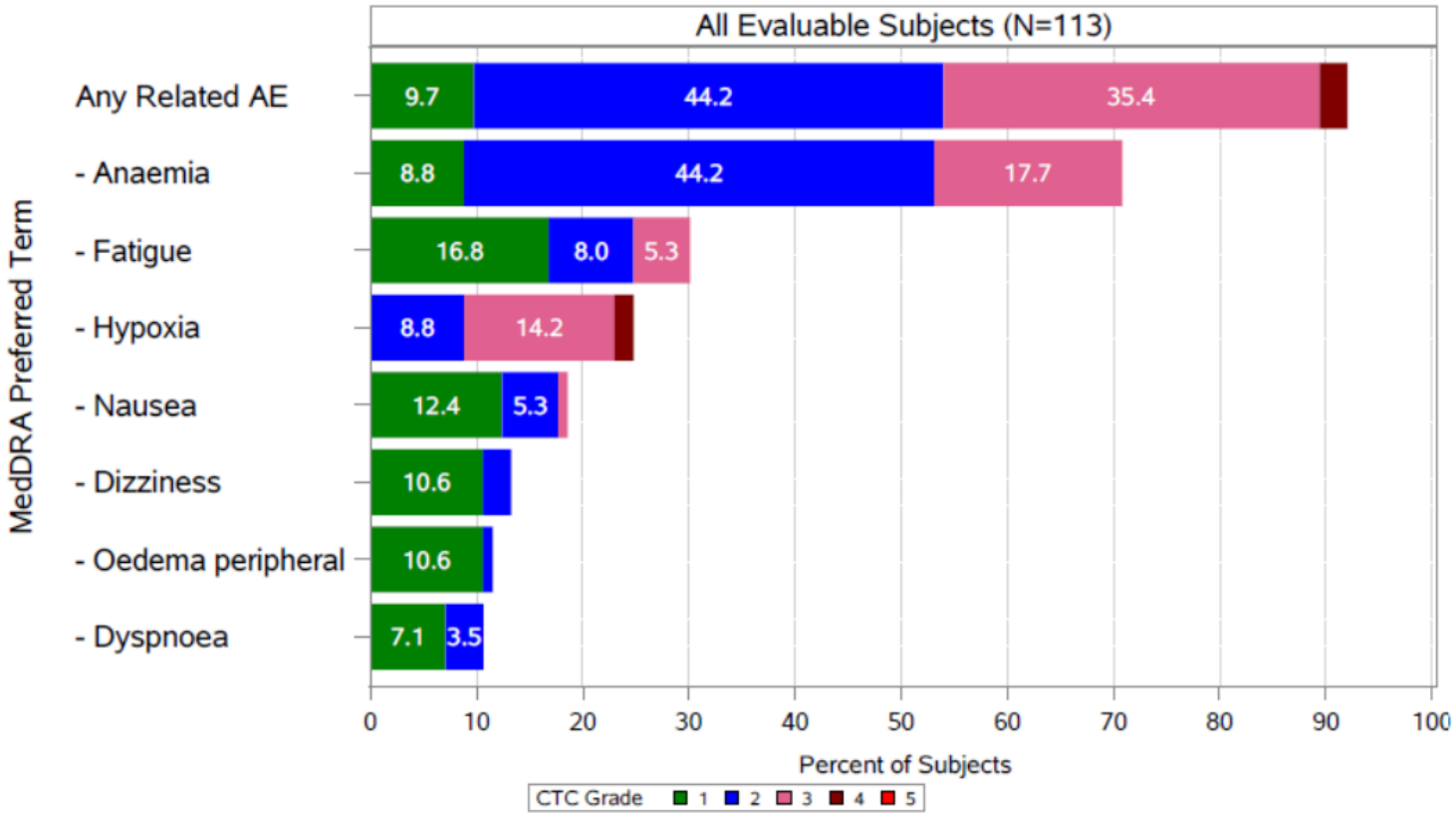
Related Adverse Events (AEs) Reported by ≥10% Subjects



The pattern of related AEs was similar across all dose levels.

Dose-limiting toxicity:

- Fatigue & Hypoxia in 1/12 subjects at 200mg QDx14, then 50mg QD
- Fatigue & Hypoxia in 1/9 subjects at 200mg QDx28, then 50mg QD

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Eric Jonasch, MD

Designated Comprehensive Cancer Center

Jonasch; ESMO 2024

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ARC-20 is a Phase 1 Dose-Escalation and Dose-Expansion Study of Casdatifan

KEY INCLUSION CRITERIA

- At least 1 measurable lesion per RECIST v1.1
- Adequate organ and marrow function

Dose Escalation

PATIENTS WITH ADVANCED SOLID TUMORS

Casdatifan monotherapy

- 200 mg QD
- 150 mg QD
- 50 mg BID
- 50 mg QD
- 20 mg QD

Dose Expansion

N = ~30 per cohort

- **2L+ ccRCC Casdatifan mono 50 mg BID capsule**
- **2L+ ccRCC Casdatifan mono 50 mg QD capsule**
- **2L+ ccRCC Casdatifan mono 100 mg QD tablet**
- 2L+ ccRCC Casdatifan mono 150 mg QD
- Post-IO ccRCC Casdatifan 100 mg QD + Cabozantinib 60 mg QD
- Favorable-risk 1L ccRCC Casdatifan mono 100 mg QD
- 1L ccRCC Casdatifan 100 mg QD + Zimberelimab 360 mg Q3W
- Post-IO ccRCC Casdatifan mono 100 mg QD

PRIMARY OUTCOMES:
AEs
DLTs

SECONDARY OUTCOMES:
ORR[a]
PK/PD

EXPLORATORY OUTCOMES:
PFS
OS
Biomarkers

1L, first-line treatment setting; 2L+, second-line treatment setting or greater; DLT, dose-limiting toxicity; IO, immunotherapy.
[a]Assessed by the investigator according to RECIST v1.1.

PRESENTED BY: Toni K Choueiri, MD

Baseline Characteristics in Patients With ccRCC Treated With Casdatifan

Safety-Evaluable Population[a]	50 mg BID (n = 33)	50 mg QD (n = 31)	100 mg QD (n = 29)
Age, years, median (range)	62 (41–79)	65 (43–82)	60 (45–77)
Sex, female/male, n (%)	8 (24) / 25 (76)	10 (32) / 21 (68)	4 (14) / 25 (86)
ECOG PS 0/1, n (%)	16 (49) / 17 (52)	18 (58) / 13 (42)	14 (48) / 15 (52)
IMDC risk score, n (%)[b]			
Favorable	10 (30)	8 (26)	6 (21)
Intermediate	21 (64)	17 (55)	19 (66)
Poor	2 (6)	5 (16)	3 (10)
Number of regimens, all settings, n (%)			
1	**2 (6)**	**5 (16)**	**5 (17)**
2+	**31 (94)**	**26 (84)**	**24 (83)**
Patients with both VEGFR-TKI and PD-1/PD-L1 inhibitor, n (%)	33 (100)	31 (100)	29 (100)

Data cutoff date: 03 January 2025.
Baseline is defined as the last nonmissing assessment before the first dosing of treatment.
[a]The safety-evaluable population included all dose expansion enrolled patients who received any amount of study treatment.
[b]One patient in the 50 mg QD group had an unknown IMDC risk score and one patient in the 100 mg QD group had a missing IMDC risk score.

Treatment With Casdatifan Showed Meaningful Clinical Activity and Disease Control Across Doses

Efficacy-Evaluable Population[a]	50 mg BID (n = 32)	50 mg QD (n = 28)	100 mg QD (n = 27)
Median follow-up, mo (range)	15 (7–19+)	12 (9–14+)	5 (2–6+)
Confirmed ORR, % (n) (95% CI)	**25% (8) (11.5, 43.4)**	**29% (8) (13.2, 48.7)**	**33% (9) (16.5, 54.0)**
Best Overall Response[b], n (%)	10 (31%)	9 (32%)	9 (33%)
CR	0	1 (4%)	0
PR	10 (31%)	8 (29%)	9 (33%)
SD	16 (50%)	15 (54%)	14 (52%)
PD	6 (19%)	4 (14%)	2[c] (7%)

Data cutoff date: 03 January 2025.
[a]All eligible patients who received any study treatment and have at least one post-baseline efficacy assessment or discontinued study treatment due to progressive disease or death.
[b]Unconfirmed best overall response.
[c]In addition to the two patients with radiological progressive disease, 2 patients had clinical progression before first scan.

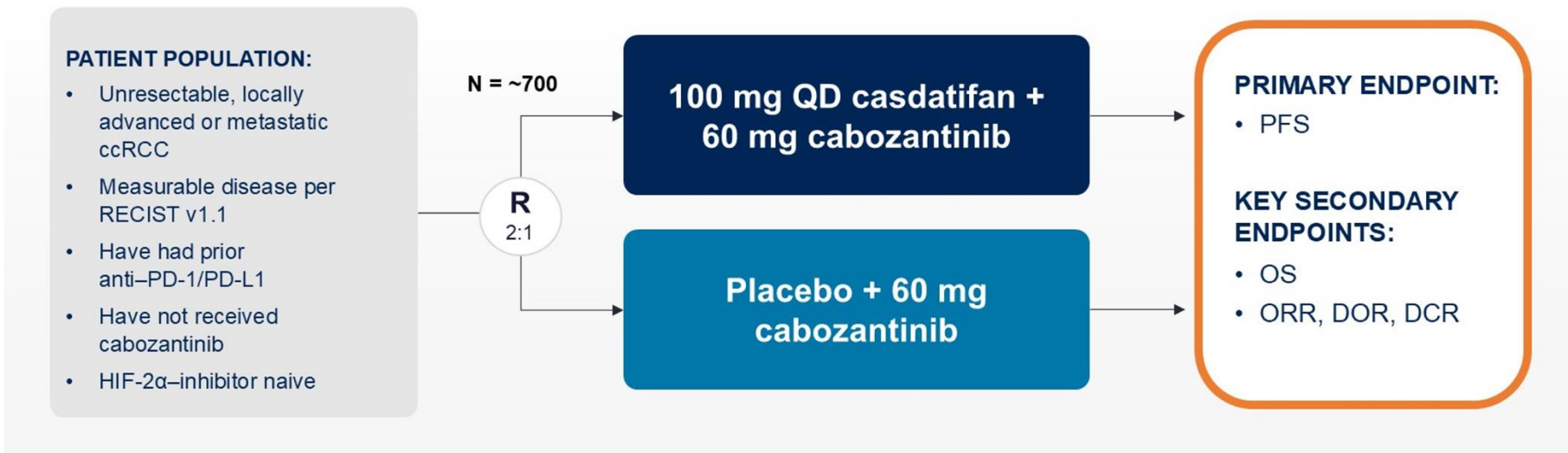
Casdatifan Was Well Tolerated With a Comparable Safety Profile Across Doses

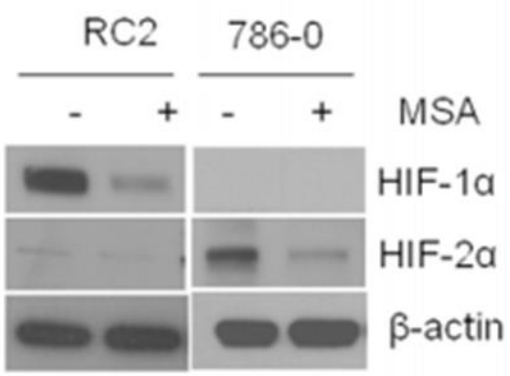
Safety-Evaluable Population[a]	50 mg BID (n = 33)	50 mg QD (n = 31)	100 mg QD (n = 29)
Median follow-up, months (range)	15 (7–19+)	12 (9–14+)	5 (2–6+)
Any TEAEs, n (%)	32 (97)	30 (97)	28 (97)
Related to casdatifan	31 (94)	28 (90)	27 (93)
Any grade ≥ 3 TEAEs, n (%)	17 (52)	16 (52)	12 (41)
Related to casdatifan	16 (49)	10 (32)	8 (28)
Any serious TEAEs, n (%)	5 (15)	9 (29)	7 (24)
Related to casdatifan	1 (3)	3 (10)	2 (7)
Anemia, n (%)			
All grades	29 (88)	28 (90)	23 (79)
Grade ≥ 3 related to casdatifan	14 (42)	10 (32)	5 (17)
Related to casdatifan leading to interruptions	11 (33)	10 (32)	6 (21)
Leading to dose reductions	2 (6)	1 (3)	0
Leading to discontinuation	**0**	**1 (3)**	**0**
Hypoxia, n (%)			
All grades	5 (15)	4 (13)	4 (14)
Grade ≥ 3 related to casdatifan	3 (9)	2 (7)	3 (10)
Related to casdatifan leading to interruptions	5 (15)	3 (10)	2 (7)
Leading to dose reductions	0	0	0
Leading to discontinuation	**0**	**1 (3)**	**1 (3)**

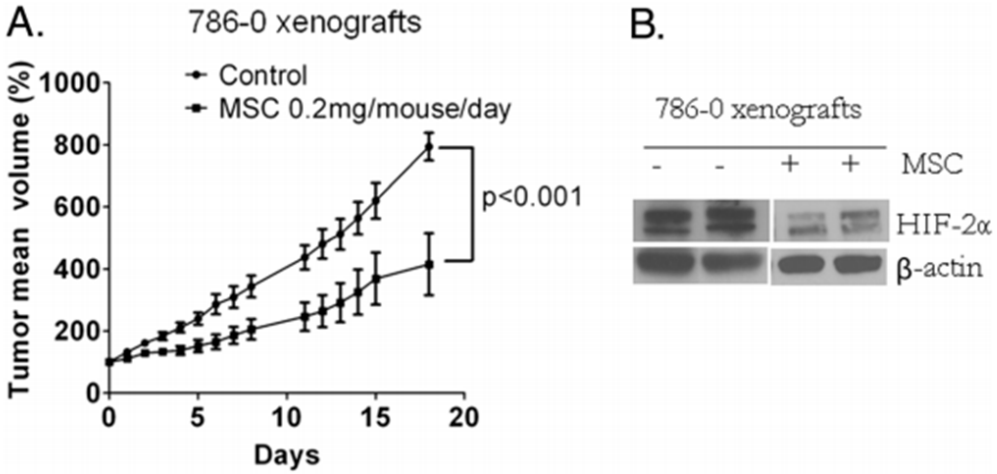
Data cutoff date: 03 January 2025.
[a]The safety-evaluable population included all dose expansion enrolled patients who received any amount of study treatment.
TEAEs, treatment-emergent adverse events.

Anticipated first half 2025

PEAK-1







a. Chintala et al. 2012
b. Durrani et al, 2015

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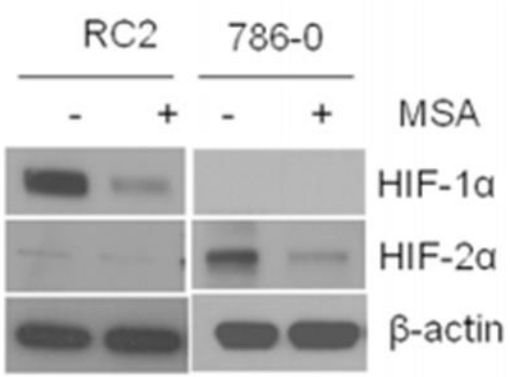

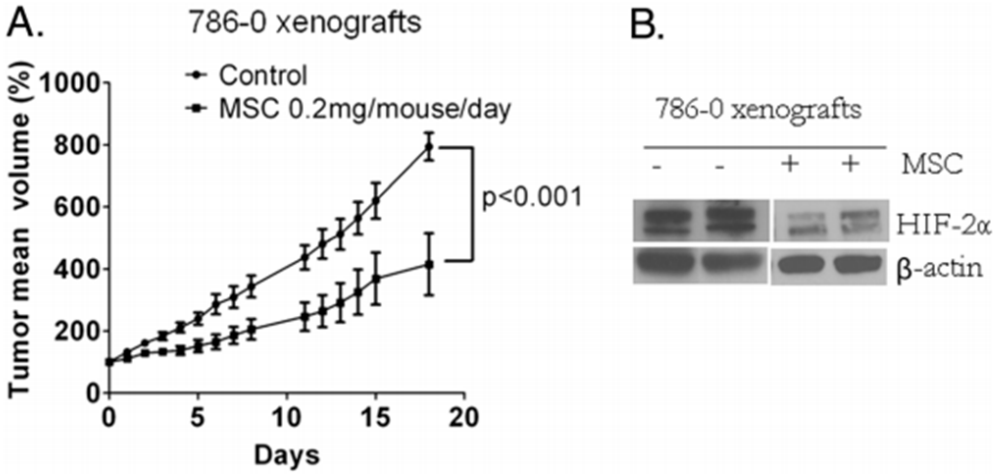

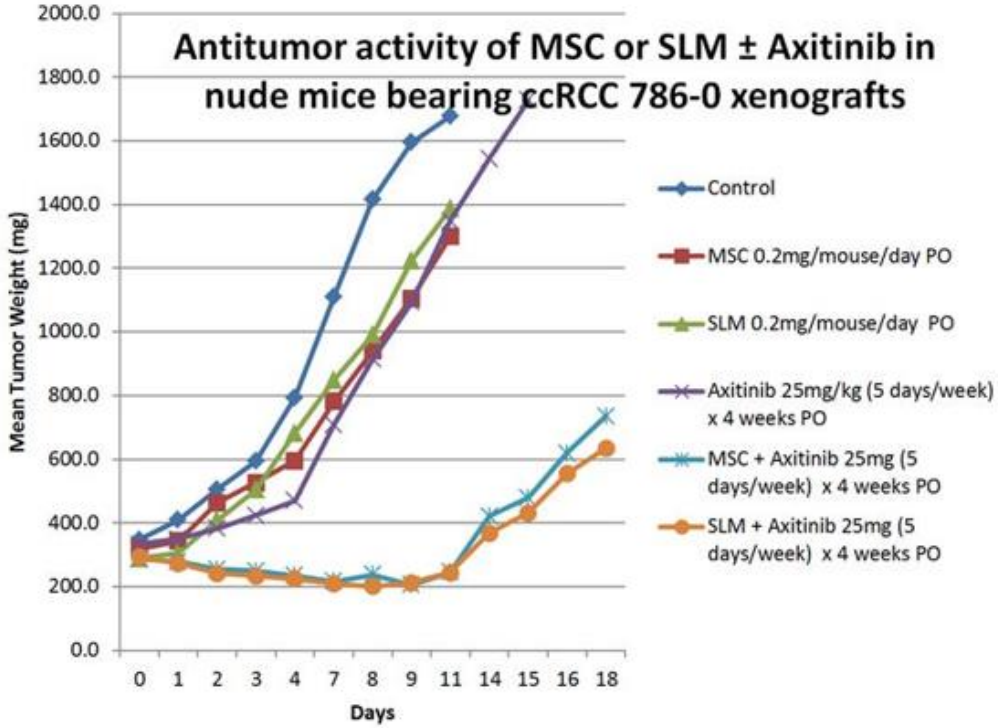

a. Chintala et al. 2012
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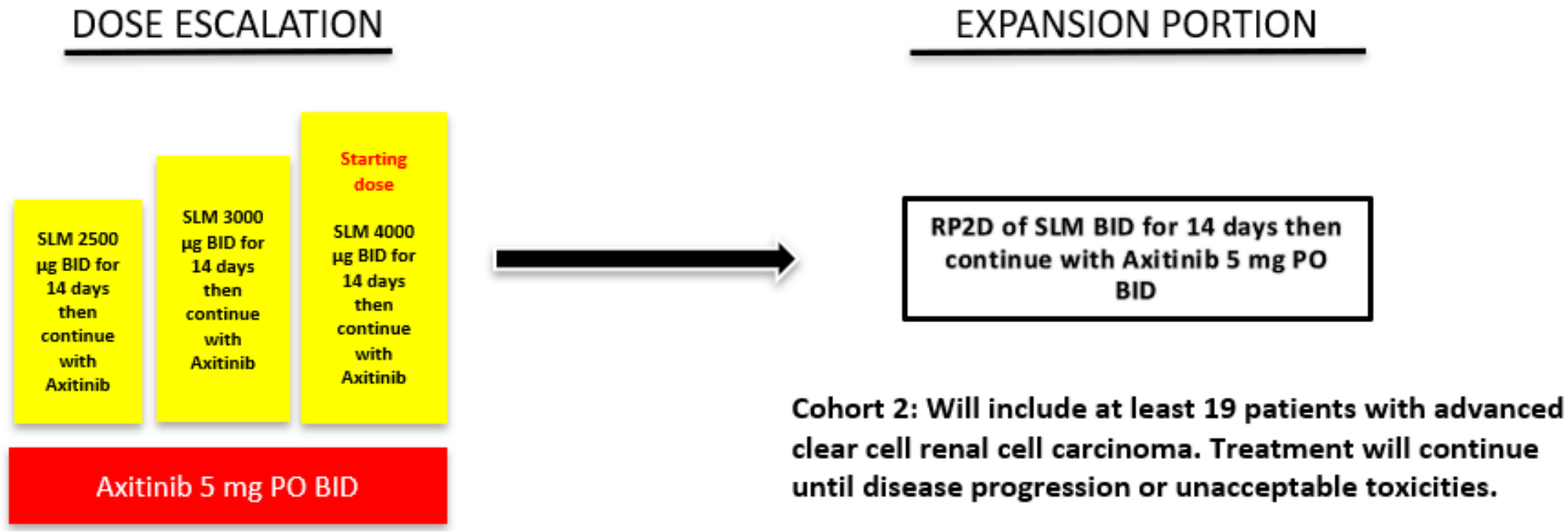
Trial Design (NCT02535533)



Adult patients with histologically-proven ccRCC and imaging confirmation of advanced disease are included. All patients are scheduled for a baseline and day 14 blood draw for miRNA studies via PCR, and up to 10 patients will complete baseline and day 14 biopsies for HIFs/VEGF and miRNA data.

Variable	*N* = 27
Age, median (min–max)	61 (39–76)
Sex, *n* (%)	
Female	4 (14.8%)
Male	23 (85.2%)
Eastern Cooperative Oncology Group performance status, *n* (%)	
0	21 (77.8%)
1	6 (22.2%)
Race or ethnic group, *n* (%)	
White	26 (96%)
Black	1 (4%)
IMDC risk group, *n* (%)	
Favorable	6 (22.2%)
Intermediate	17 (63.0%)
Poor	4 (14.8%)
Sarcomatoid features, *n* (%)	3 (11.1%)
Prior systemic therapies, median (min–max)	2 (1–4)
Prior systemic therapies, *n* (%)	
1	13 (48.1%)
2	9 (33.3%)
≥3	5 (18.5%)
Prior anticancer therapies[a], *n* (%)	
Ipilimumab + nivolumab	11 (40.7%)
Nivolumab	6 (22.2%)
Pazopanib	6 (22.2%)
Cabozantinib	6 (22.2%)
Sunitinib	5 (18.5%)
Durvalumab + guadecitabine	5 (18.5%)
Everolimus	3 (11.1%)
Sunitinib + AGS-003	2 (7.4%)
Axitinib + TRC105	1 (3.7%)
Axitinib + X4P	1 (3.7%)
IL-2	1 (3.7%)

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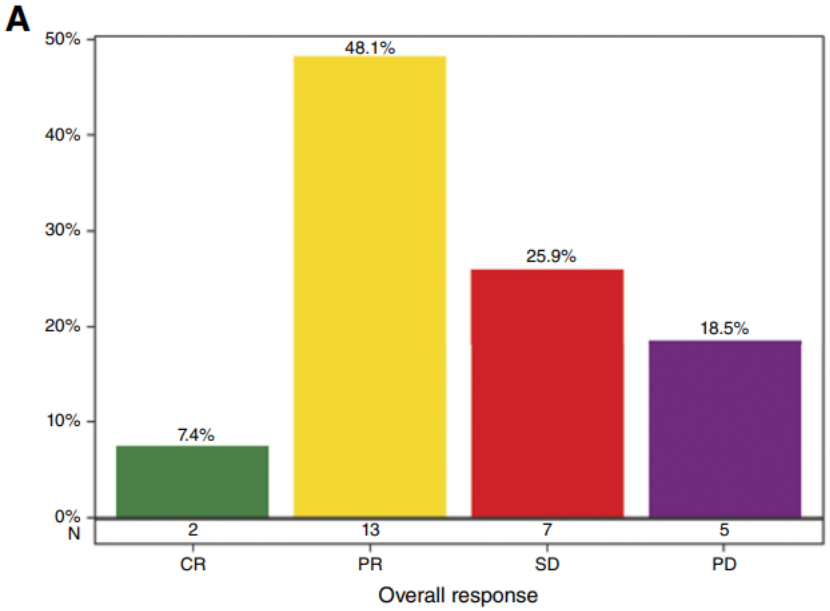

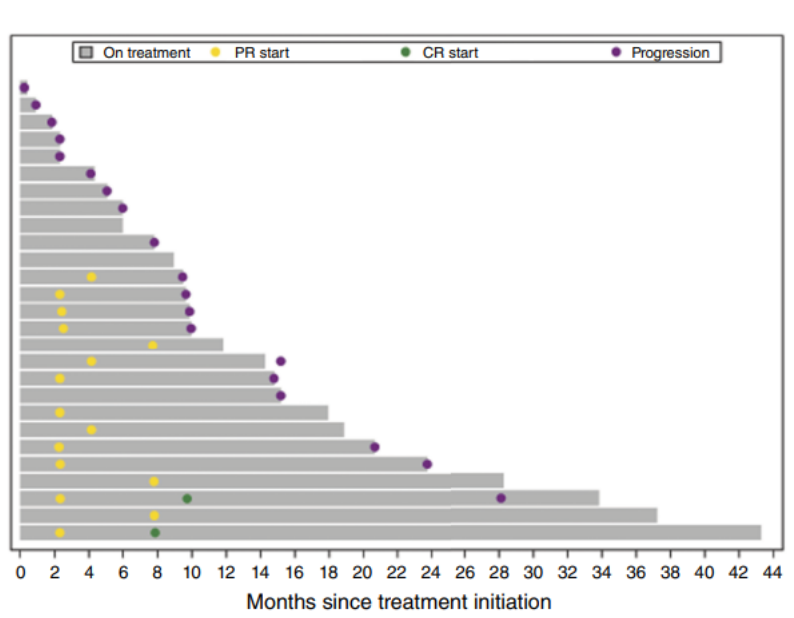

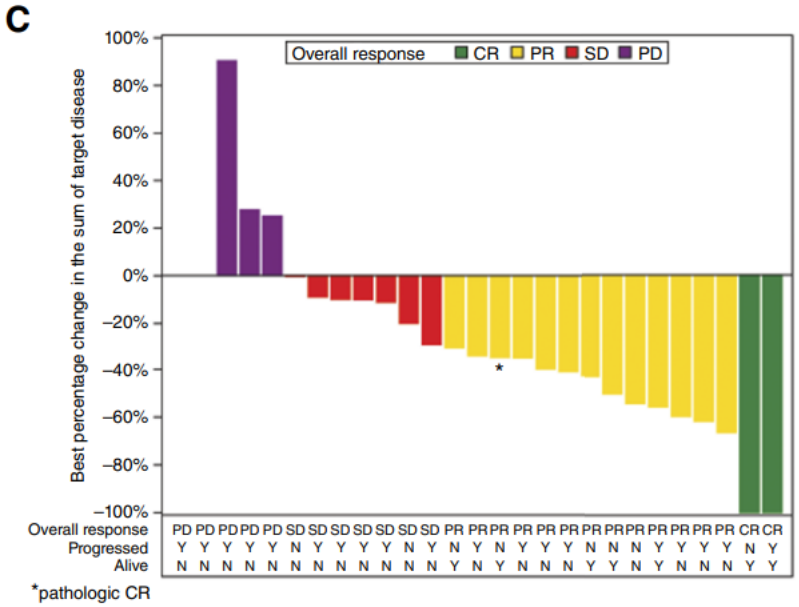

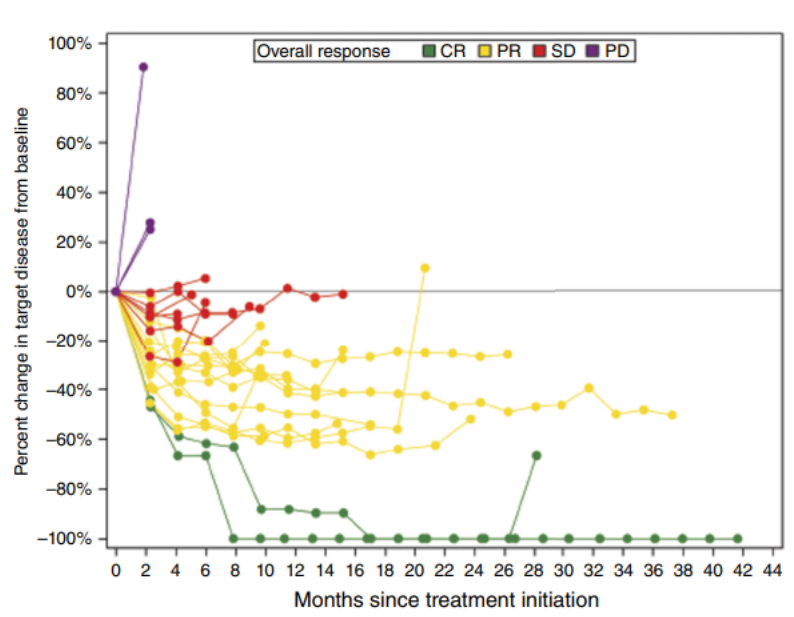

Median PFS: 14.8 months (95% CI, 6.0–20.7)
Median OS: 19.6 months (95% CI, 12.0–40.6

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Closing Remarks

- HIF 2a important pathway in RCC
- Consistent safety and tolerability
- Perhaps earlier in the course of treatment
- Awaiting LITESPARK-012 if would position in 1st line setting

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I REMAIN MUCH MORE EXCITED ABOUT MY SLM IIT

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Thank you!

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