

#guardsymposium2026
X @GuardConsortium



Novel Targets in RCC

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Four strategies to break through the IO + TKI plateau

01

HIF-2 α

Oral inhibition, combinations, gatekeeper resistance and the ferroptosis paradox

02

Surface antigens

ENPP3 and CD70: T-cell engagers and allogeneic CAR-T

03

Emerging targets

Logic gates, HLA-G, HERV-E, KIM-1/CDH6 and TROP-2 in papillary RCC

04

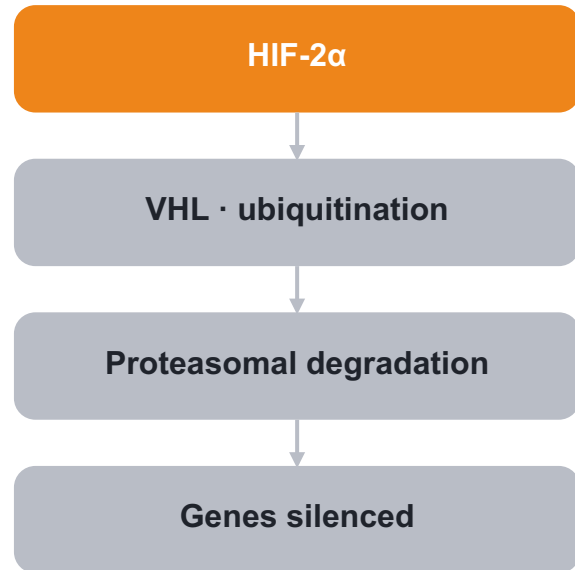
Theranostics & organ-directed

Radiolabeled CAIX and orellanine

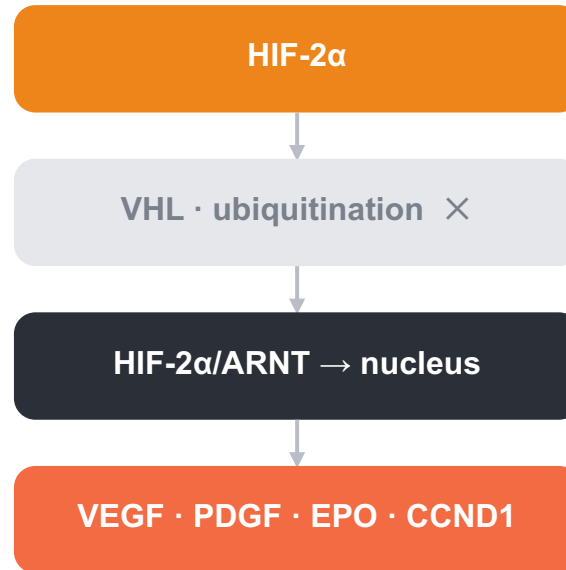
HIF-2 α

VHL loss stabilizes HIF-2 α and constitutively activates the hypoxic program

FUNCTIONAL VHL (normal tissue)



INACTIVATED VHL (ccRCC)



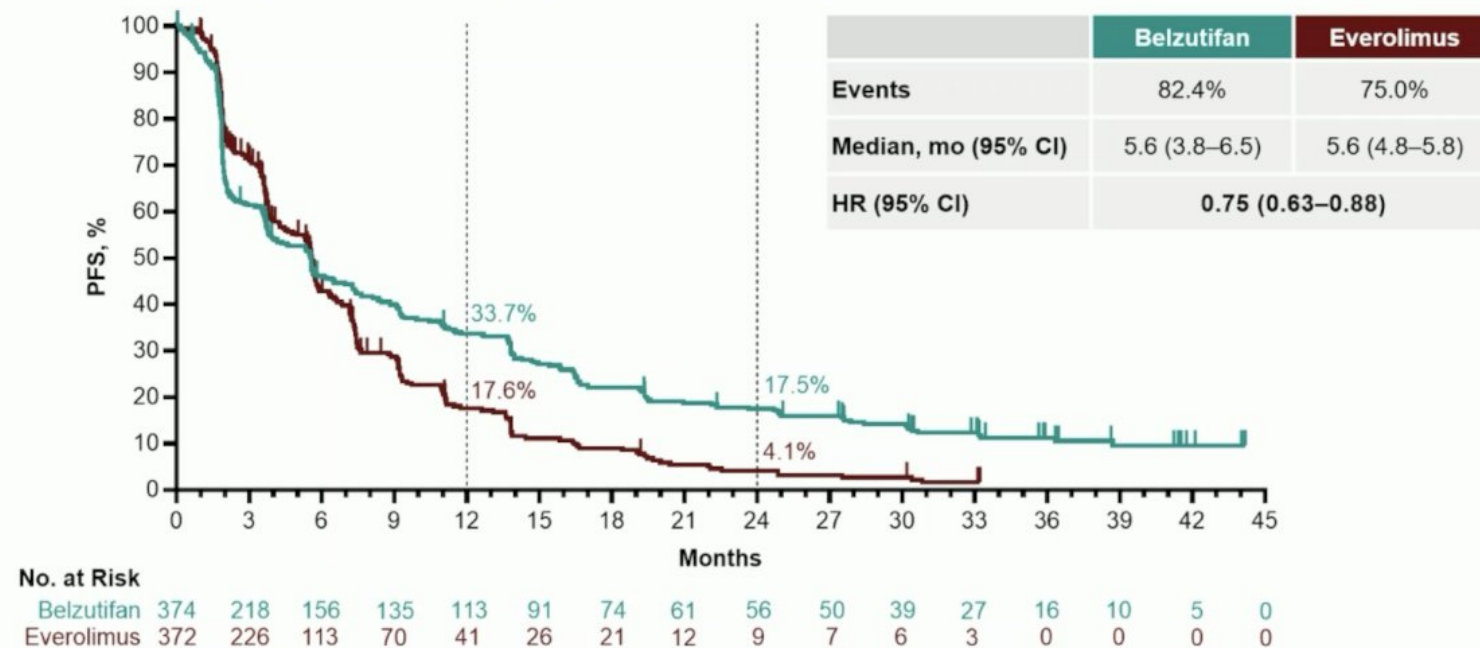
>80–90% of ccRCCs harbor VHL inactivation; HIF-2 α acts as the dominant oncogene.

Direct blockade: belzutifan and casdatifan occupy an internal cavity of HIF-2 α and prevent dimerization with ARNT.

Class biomarker: renal EPO depends on HIF-2 α ; its suppression explains the anemia and serves as a pharmacodynamic marker.

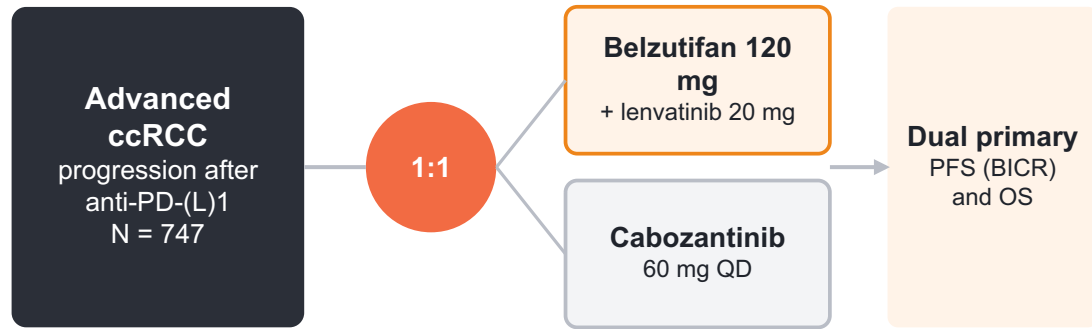
LS-005: Impact on PFS, not OS

Primary Endpoint: PFS per RECIST 1.1 by BICR



Belzutifan + lenvatinib prolongs PFS vs cabozantinib after anti-PD-(L)1

STUDY DESIGN



HR 0.70

PFS · 95% CI
0.59–0.84

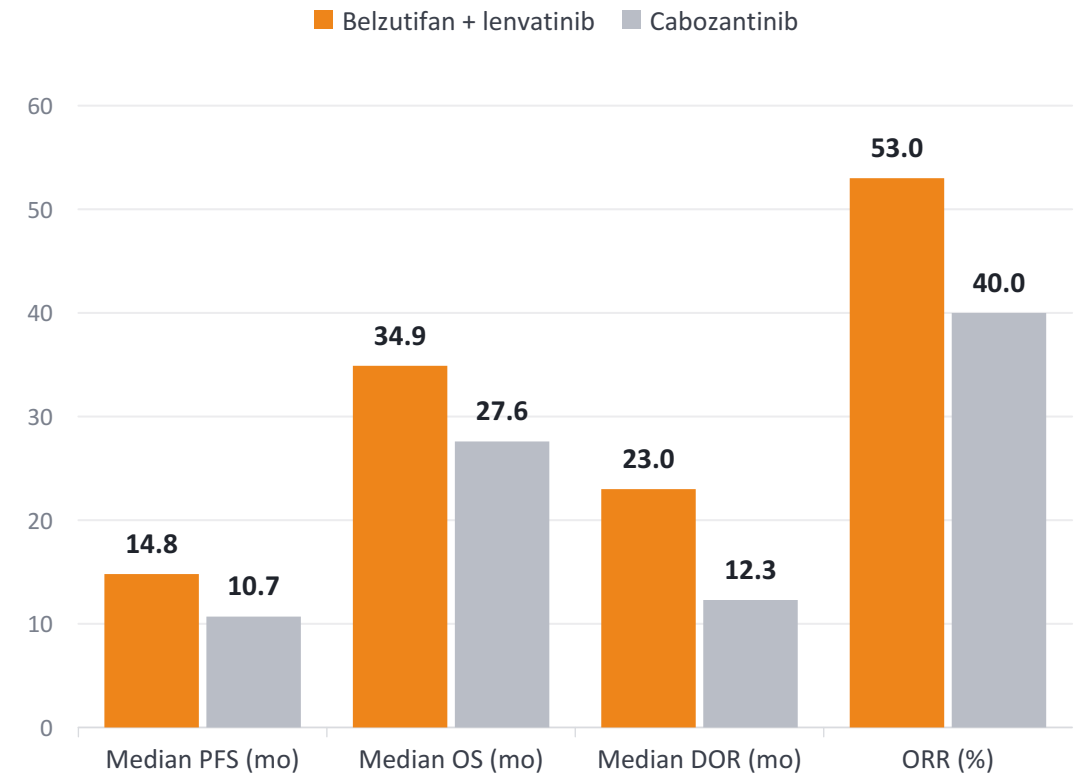
HR 0.85

OS · p=0.061 (not
significant)

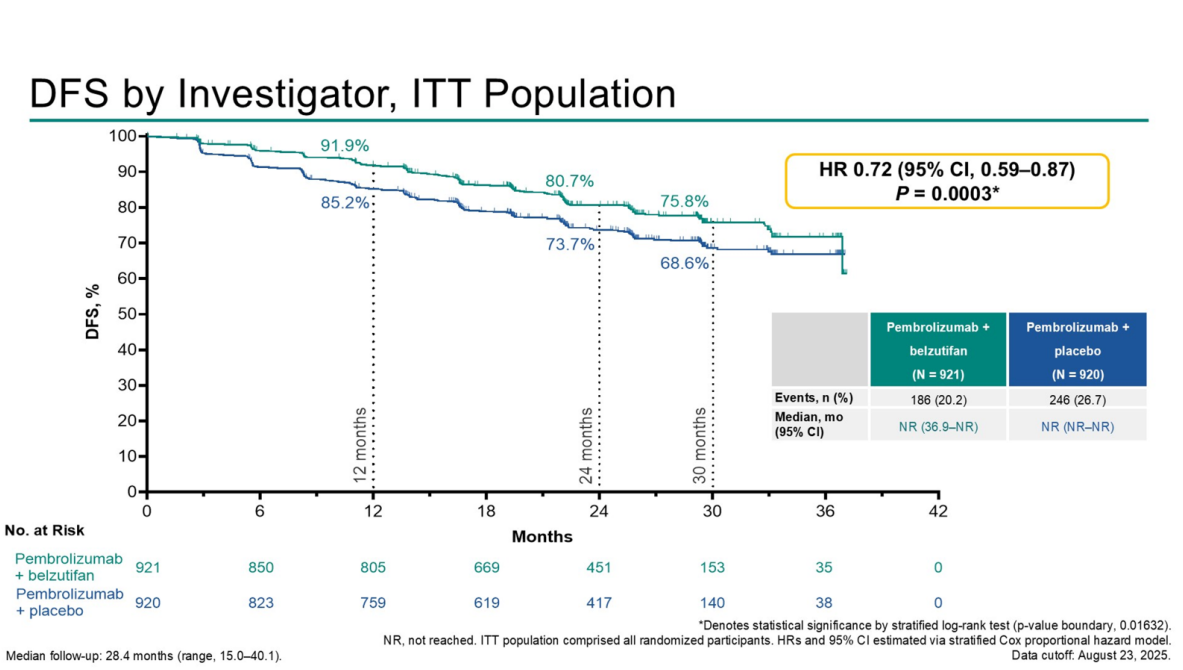
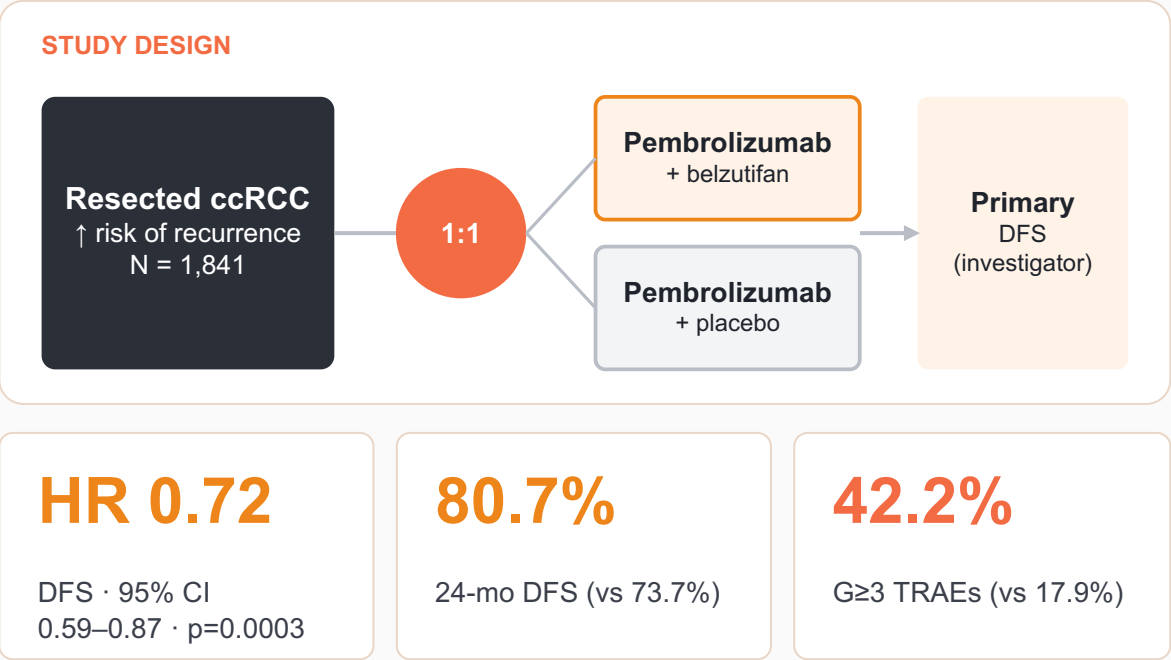
Oct 4, 2026

FDA decision date

Second interim analysis, median follow-up 29 months. OS follow-up continues per protocol.



First positive adjuvant trial against an active immunotherapy comparator

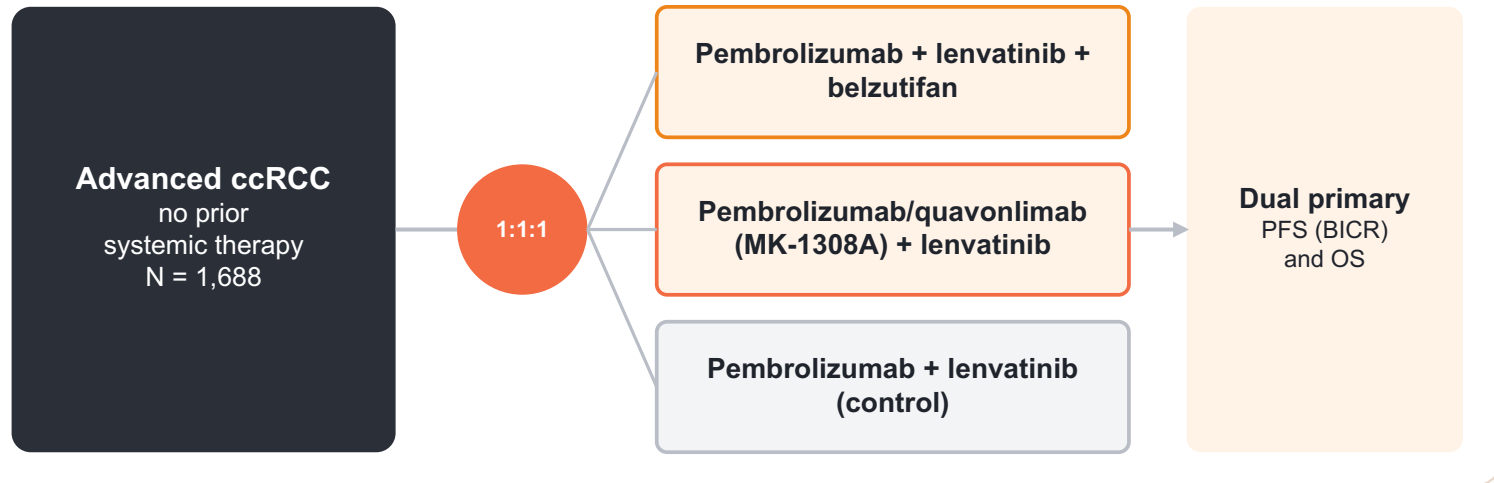


Anemia in 84% (G≥3 12.1%) and G≥3 hypoxia 4.6%. OS immature and not significant at the first interim analysis.

Choueiri TK et al. ASCO GU 2026

Triplet intensification does not improve 1L PFS or OS

STUDY DESIGN



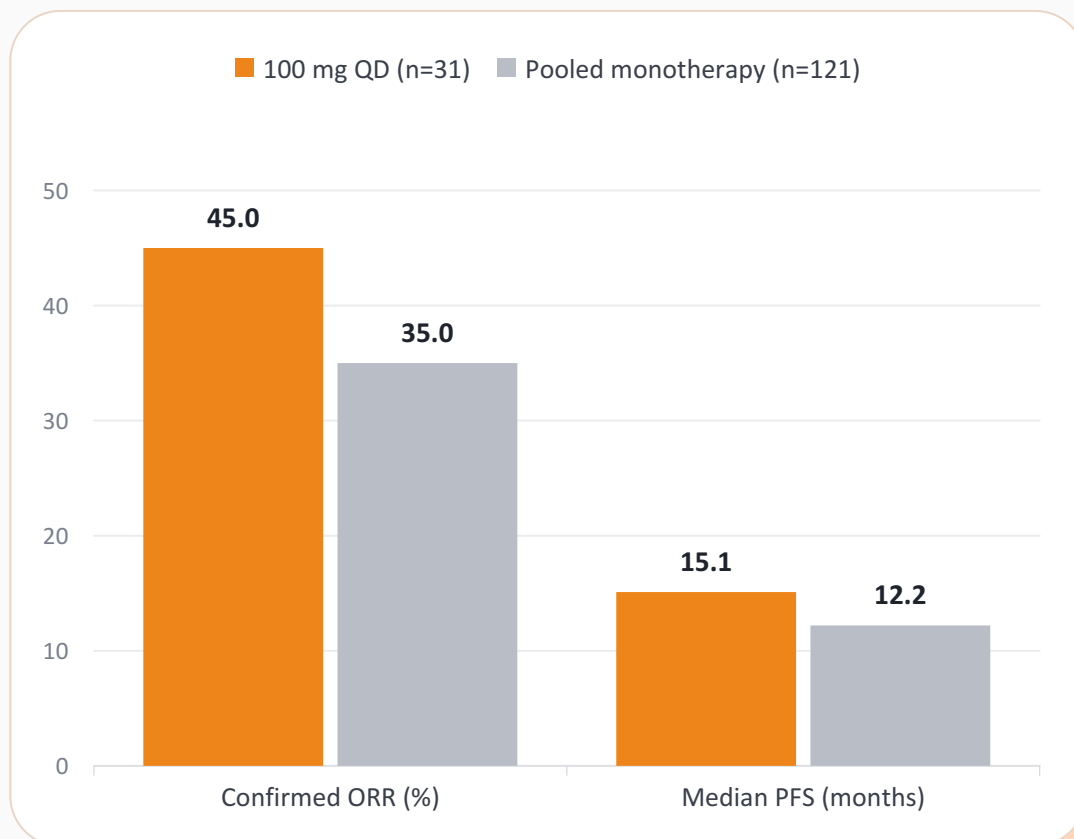
OUTCOME

Neither experimental arm met the dual primary endpoints

Prespecified interim analysis. Safety consistent with the individual agents.

Implication: adding a third active drug to a highly active doublet is not automatically superior. The value of HIF-2α depends on the setting and the combination partner.

Casdatifan monotherapy: durable responses



68%

Maximal serum EPO suppression >80%, associated with higher response and longer PFS

89%

Anemia (G $\geq$ 3 41%) · class effect

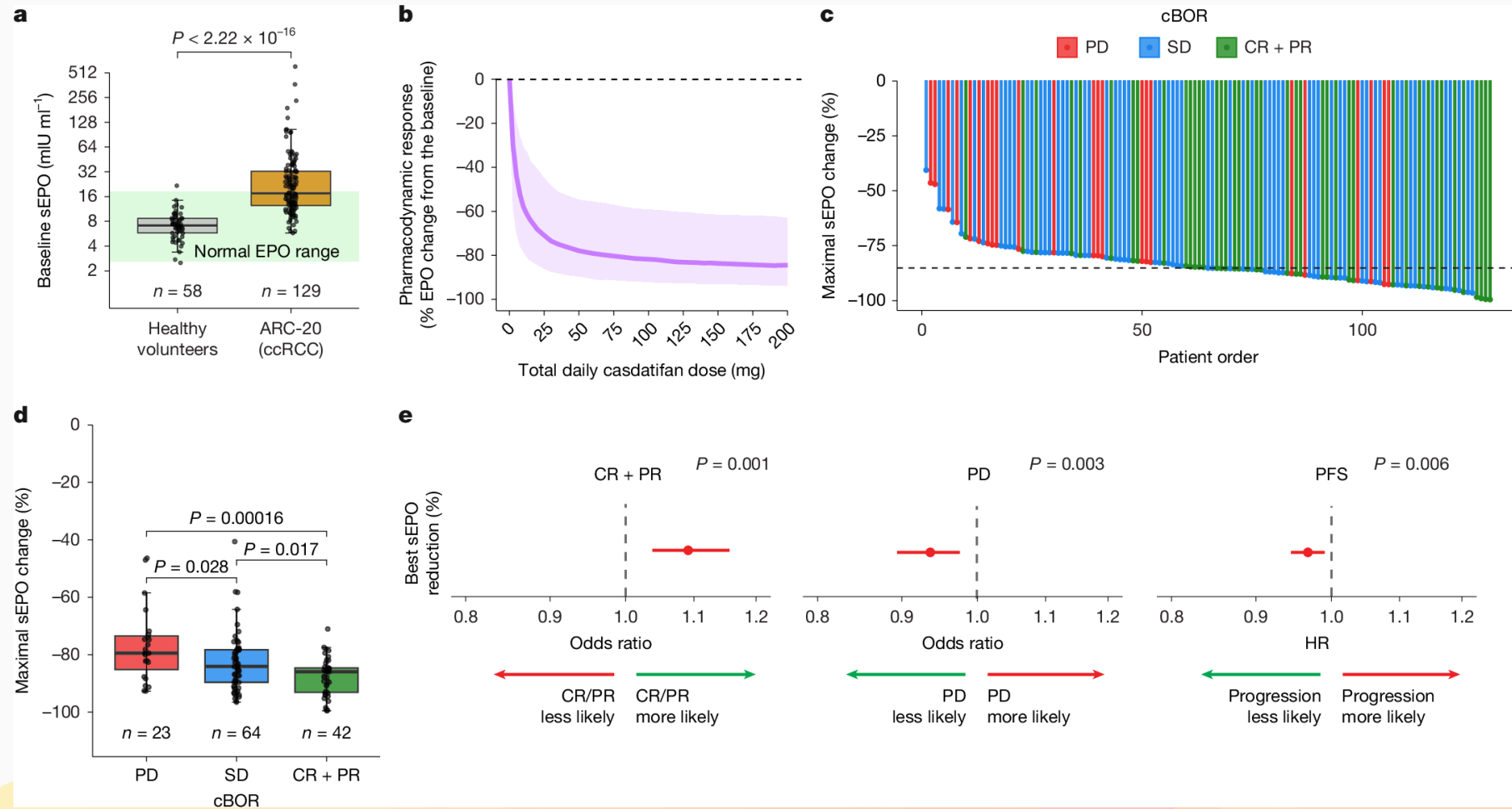
Population: metastatic ccRCC pretreated with IO and TKI.

Hypoxia 16%; discontinuation due to adverse events 9%.

Biology: a high HIF-2 α transcriptional signature was associated with longer PFS (HR 0.43).

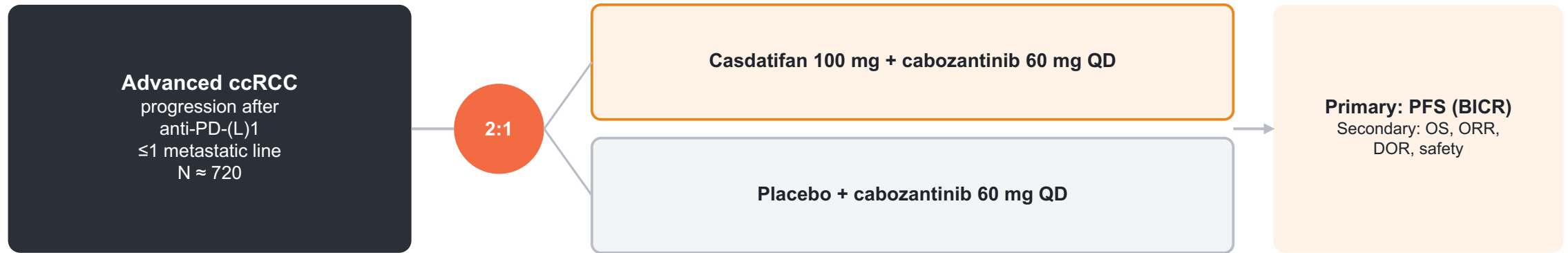
Next step: phase 3 PEAK-1 with the 100 mg dose and formulation.

Casdatifan monotherapy: correlation with EPO suppression



PEAK-1: casdatifan + cabozantinib vs cabozantinib after anti-PD-(L)1

STUDY DESIGN



Double-blind

No crossover allowed

Stratification

Region · prior VEGFR-TKI · IMDC risk

Key exclusion

Prior HIF-2α inhibitor or cabozantinib

Timeline

Started Sept 2025

EPAS1 G323E: HIF-2 α inhibition now has a gatekeeper resistance mutation

Finding: sequencing of baseline and post-progression samples revealed emergence of the somatic **EPAS1** p.G323E mutation.

Mechanism: a gatekeeper mutation inside the PAS-B pocket that prevents drug-induced dissociation of the HIF-2 α :ARNT complex.

Second route: F446L in ARNT. Belzutifan and its analogues share a binding mode, so they are expected to be equally affected.

Implication: class resistance: inhibitors with new chemotypes, directed at different pockets, are needed.

WE HAVE JUST RECREATED T790M

Gatekeeper

Drug still binds, but the dimer no longer comes apart

Class resistance

A structurally distinct second generation is required

The whole kinase playbook, applied to a transcription factor — and the reason a degrader, not a better inhibitor, is the logical next move.

BMS-986506: a cereblon modulator (CELMoD) enters phase 1 in ccRCC

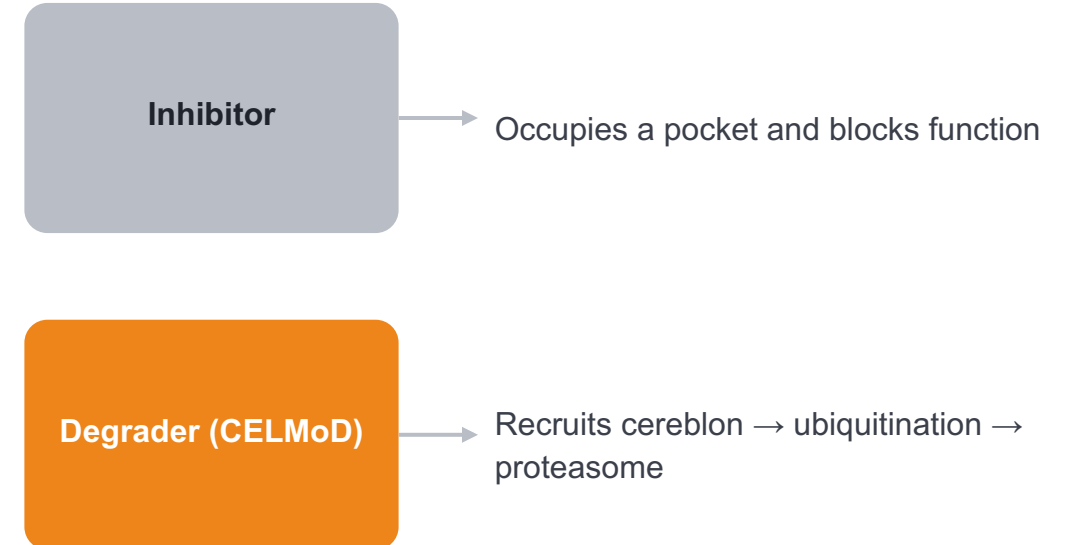
Mechanism: CELMoD agent that modulates the E3 ligase cereblon to induce targeted protein degradation. The target substrate has not been publicly disclosed.

Design: open-label, multicenter phase 1/1b, as monotherapy and in combination.

Endpoints: safety, DLTs and pharmacokinetics; secondary ORR, DCR and duration of response per RECIST 1.1.

Context: arising from the BMS–Evotec protein degradation collaboration; first patient dosed in 2026.

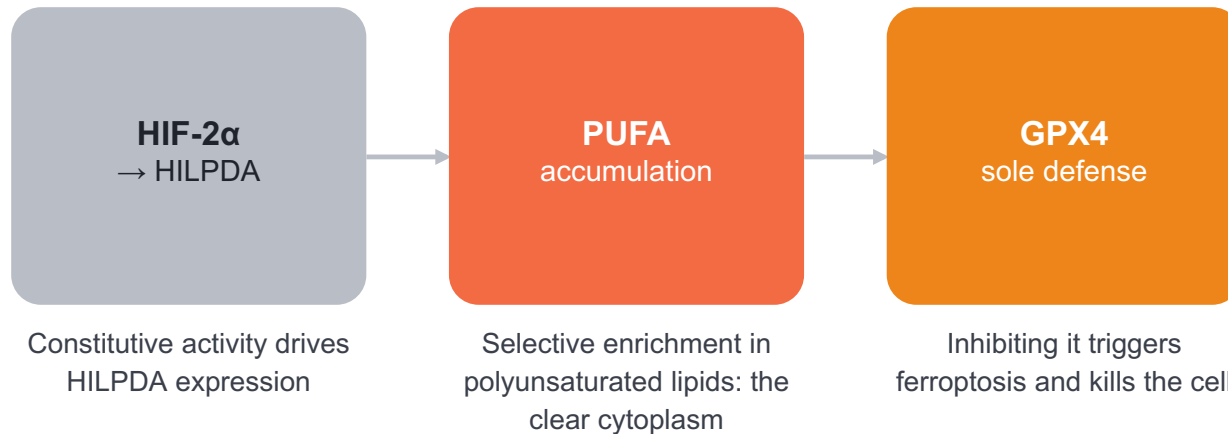
INHIBIT VS DEGRADE



Conceptual paradox: ccRCC arises from the loss of an E3 ligase (VHL).

GPX4: in clear cell RCC the morphology is the target

FROM VHL LOSS TO A LETHAL DEPENDENCY



Screening: in the CTRP, three GPX4 inhibitors (RSL3, ML210, ML162) emerged as the most potent and selective compounds killing clear cell carcinoma lines, against the low efficacy of conventional chemotherapy such as paclitaxel in the same lines.

The paradox: HIF-2α knockout blocked the ferroptosis triggered by GPX4 depletion in 786-O cells.

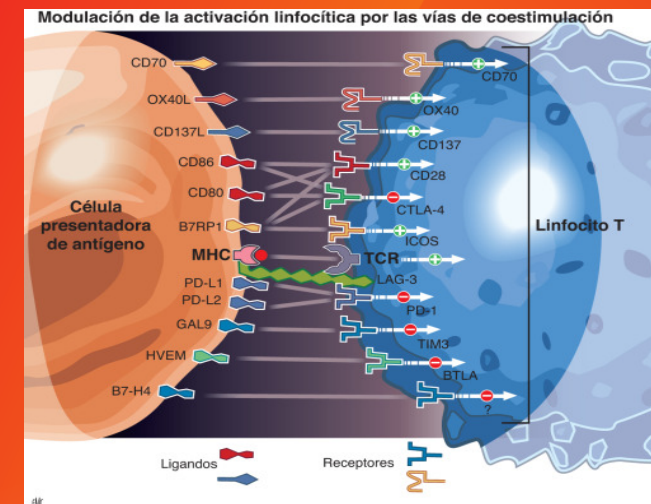
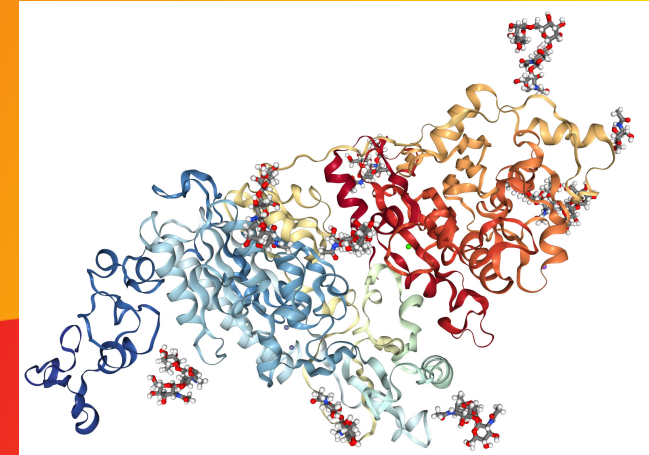
Consequence: the same axis we switch off with belzutifan or casdatifan is the one that creates the vulnerability.

Question 1: does GPX4 come before or after the HIF-2α inhibitor?

Question 2: does sequence matter more than combination?

Surface antigens

ENPP3 and CD70: redirecting T cells against the tumor



XmAb819 (ENPP3×CD3): first responses with a T-cell engager in ccRCC

XmAb 2+1 FORMAT

T cell · CD3

XmAb819

1 scFv anti-CD3 · 2 Fab anti-ENPP3

Tumor cell · ENPP3 high

25%

Partial response in target dose range (5/20)

70%

Disease control (DCR)

4 lines

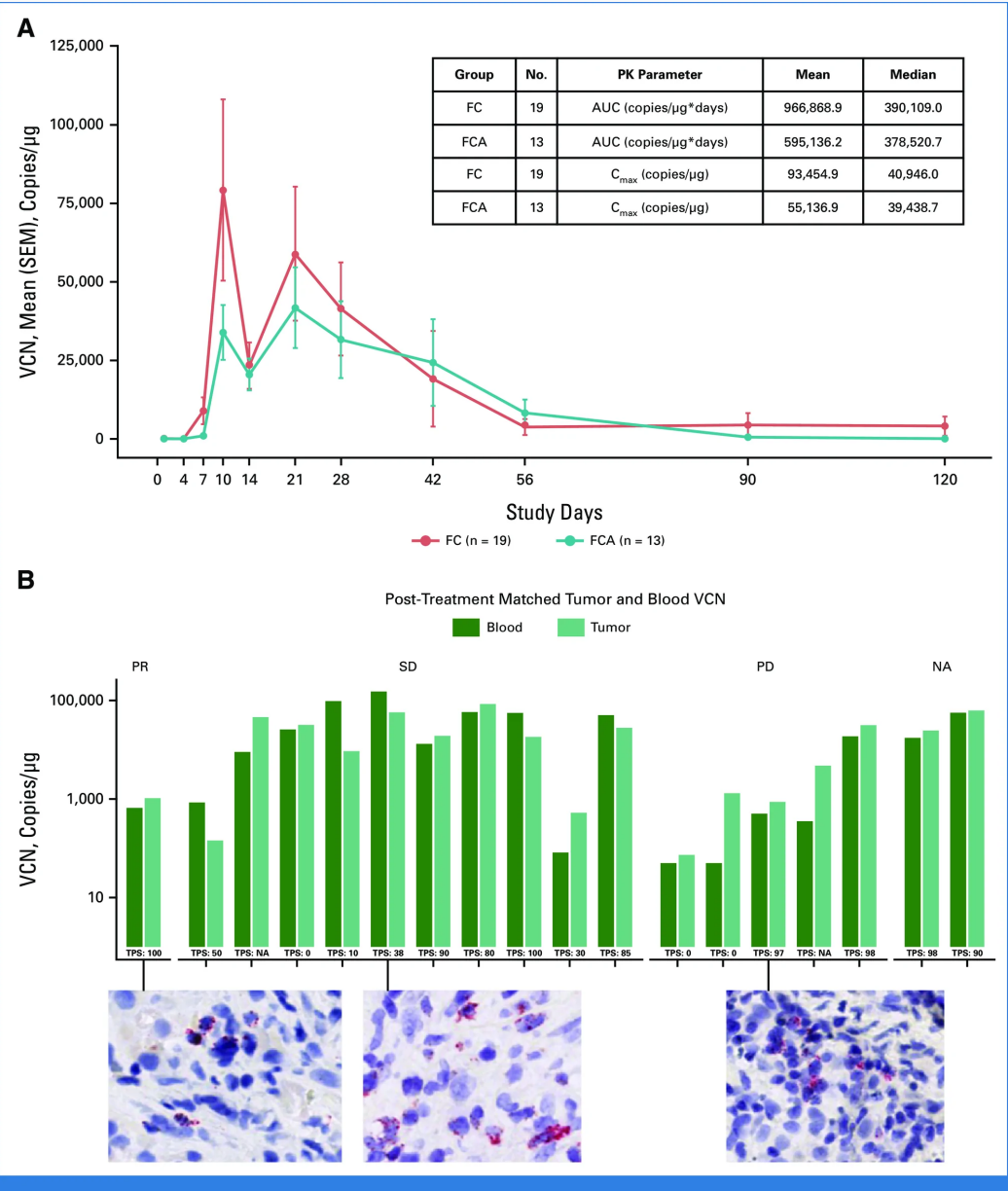
Median prior therapies (range 1–8) · N=69

Durability: all 5 responders remained on treatment at cutoff; 10/20 in the target range were still on therapy.

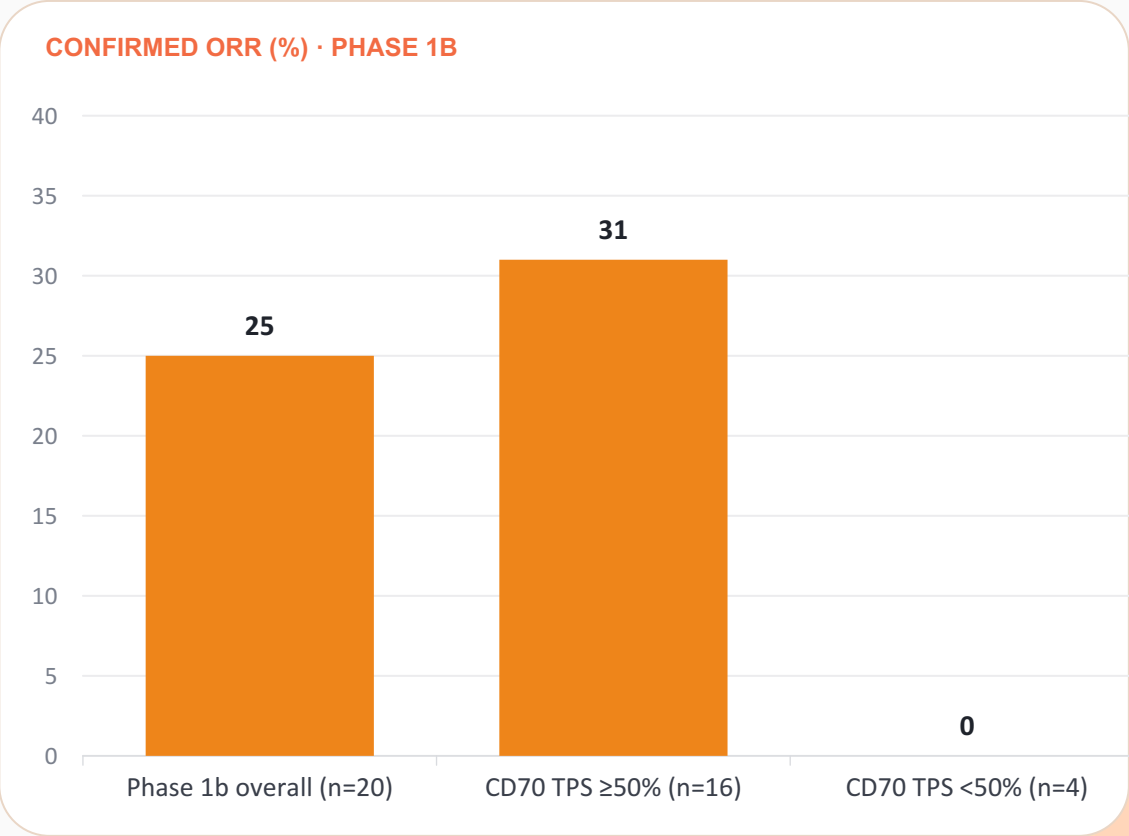
Safety: CRS mostly G1–2; no G5 events. Discontinuation due to TRAEs 4%.

Phase 1 lesson: with correct step-up dosing, G3 CRS 4%; in 18 patients with preparation errors (3–8-fold higher exposure), 28%.

ALLO-316: response to allogeneic anti-CD70 CAR-T depends on CD70 expression

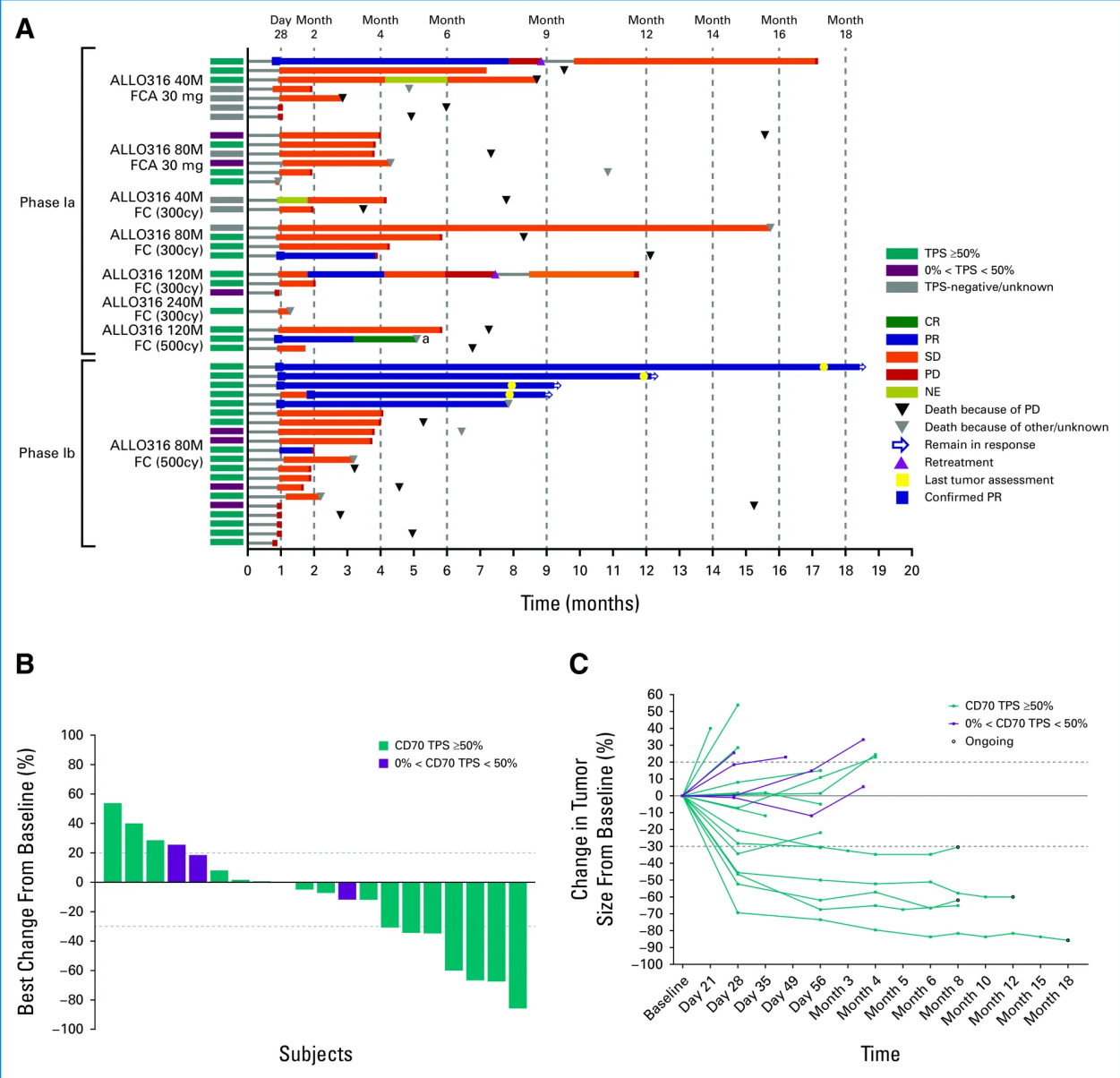


ALLO-316: response to allogeneic anti-CD70 CAR-T depends on CD70 expression



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Phase 1 TRAVERSE, J Clin Oncol, 2026;



AB-2100: a PSMA→CAIX logic gate to avoid off-tumor toxicity

SEQUENTIAL "AND" LOGIC



Additional modules: shRNA against FAS and TGFBR2 plus a synthetic pathway activator (STAT3). Cassette inserted by CRISPR into a safe-harbor locus.

Problem: a previous anti-CAIX CAR-T was limited by on-target/off-tumor toxicity.

Population: relapsed ccRCC after a checkpoint inhibitor and a VEGF inhibitor.

Design: ≈60 patients in phase 1 and ≈70 in phase 2; single infusion ± conditioning chemotherapy.

Status: first patient dosed in April 2024; no clinical data published.

Emerging targets

Immune tolerance, retroviral antigens and papillary carcinoma

IVS-3001: CAR-T targeting HLA-G, a maternal–fetal tolerance checkpoint

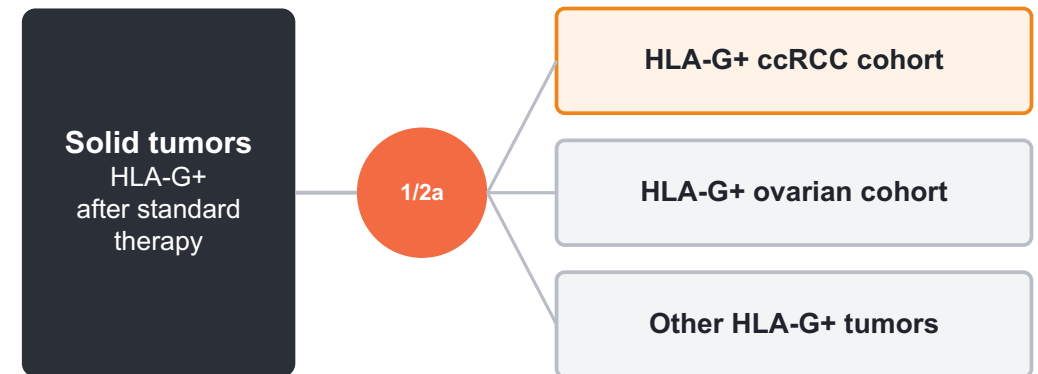
Target: HLA-G physiologically protects the fetus from the maternal immune system and is re-expressed by some tumors.

Product: autologous anti-HLA-G CAR-T developed by Invectys with MD Anderson and its Cell Therapy Manufacturing Center.

Selection: tumor HLA-G expression by immunohistochemistry.

Regimen: leukapheresis, fludarabine + cyclophosphamide and a single infusion of IVS-3001.

STUDY DESIGN



HERV-E: TCR-T targeting a ccRCC-selective endogenous retroviral antigen

19/185

Screened patients HLA-A*11 positive

No DLTs

No off-target toxicity or treatment-related deaths

7% · 29%

Partial response · stable disease ≥8 weeks

62 days

Median PFS

Origin: donor CD8+ clone from a patient with regression after allogeneic transplant, HLA-A*11-restricted.

Specificity: HERV-E is selectively expressed in most ccRCCs.

Regimen: cyclophosphamide + fludarabine, TCR-T and IL-2.

LESSON

Proof of concept of tumor regression without off-target toxicity. HLA restriction limited eligibility to ~10% of screened patients.

KIM-1 and CDH6: two targets kidney cancer found and barely uses

92.5%

Sensitivity of pre-nephrectomy plasma KIM-1 for ccRCC vs benign mass (spec. 60%)

HR 0.72

DFS with adjuvant atezolizumab in the KIM-1-high subgroup of IMmotion010 (95% CI 0.52–0.99)

MRD

KIM-1 was the most enriched serum protein at relapse vs the postoperative baseline

LT-025

Anti-KIM-1 ADC, site-specific DM1 payload (DAR 2)

KIM-1 / HAVCR1: overexpressed in proximal tubule tumors — clear cell, papillary and translocation RCC; its ectodomain is shed and measurable in plasma.

CDH6: raludotatug deruxtecan induced CDH6-level-dependent tumor regression, with lysosomal internalization and DXd release.

TROP-2 is overexpressed in papillary RCC: rationale for anti-TROP-2

ADCs

20/22

pRCC with moderate–strong
membranous expression

265

Median H-score in pRCC (IQR
202.5–290)

$\rho = 0.78$

Serum–tissue TROP-2 correlation

Caki-1

TROP-2+ cell line sensitive to
sacituzumab govitecan in vitro

Cohort: ccRCC n=44, papillary n=22, chromophobe n=22 and benign tumors n=8.

Contrast: absent or weak expression in ccRCC and chromophobe.

Enlace para SN-38

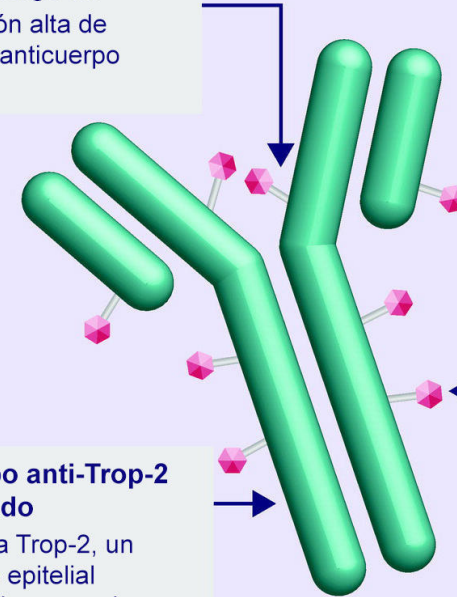
- Enlace hidrolizable que libera la carga útil
- Proporción alta de fármaco-anticuerpo (7,6:1)

Anticuerpo anti-Trop-2 humanizado

- Dirigido a Trop-2, un antígeno epitelial expresado en muchos tumores sólidos

Carga de SN-38

- Metabolito del inhibidor de Topo I
- SN-38, más potente que el compuesto original (irinotecán)



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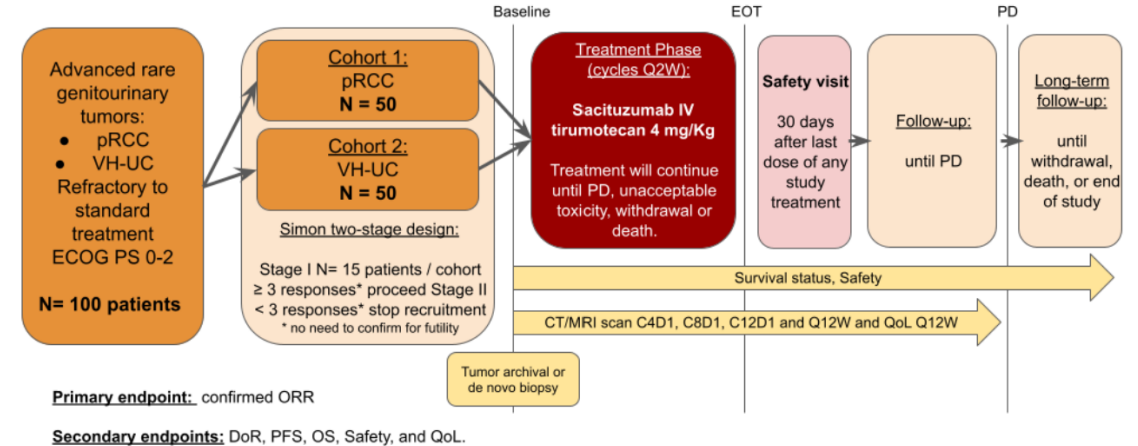
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Figure 1 Study scheme.



Theranostics and organ-directed chemotherapy

See to select, and exploit proximal tubule biology

[⁶⁸Ga]Ga-DPI-4452: CAIX-targeted theranostic pair with exceptional tumor uptake

6.8–211.6

SUVmax at 1 h in 36 lesions (mean 64.6)

17

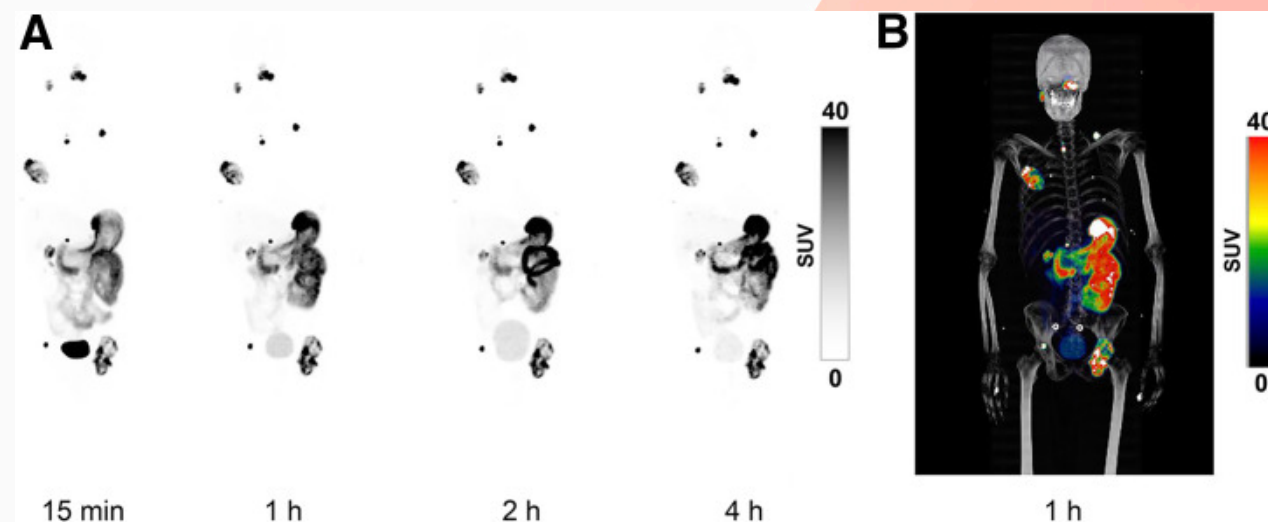
Metastases not identified by conventional imaging (3 patients)

Molecule: cyclic anti-CAIX peptide labeled with ⁶⁸Ga (imaging) or ¹⁷⁷Lu (therapy).

Biodistribution: low activity in kidney, liver and marrow; rapid blood clearance. Gastrointestinal uptake is a limitation.

Safety: no clinically significant toxicity.

2026 update: prospective study with 20 metastases undetected by conventional imaging.



THERANOSTICS: LUTETIUM-177 THERAPIES

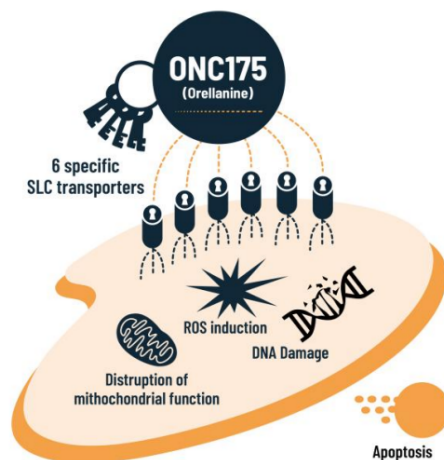
Trial / NCT	Target	Radioligand (Drug)	Phase	Key Features
DPI-4452 NCT05706129	CAIX	[177Lu]Lu-DPI-4452	Phase 1/2	Dose finding and efficacy (Parts B and C) after confirming uptake on diagnostic 68Ga-PET.
STARLITE 2 NCT05239533	CAIX	177Lu-girentuximab + Nivolumab	Phase 2	Combination Strategy: Seeks synergy between targeted radiation and Immunotherapy.
RENALUT NCT06783348	PSMA	177Lu-PSMA-617 (Pluvicto)	Phase 2	Patients progressing on IO/TKI. Open in Spain
PRadR NCT06059014	PSMA	177Lu-PSMA-1	Phase 1/2	European study (France). Assesses toxicity and response rate after 4 cycles.
LASER NCT06964958	PSMA	177Lu-PSMA-617	Phase 2	Sponsored by Dana-Farber. Evaluates systemic therapy based on vascular PSMA expression.

Orellanine (ONC175)

MECHANISM OF ACTION OF ONC175



The potent and selective renal cell toxicity of **orellanine** is the foundation for the development of ONC175 for treating patients with end-stage metastatic renal cancer



- Selective uptake of Orellanine via 8 specific soluble carrier (SLC) transporters
- Induction of oxidative stress
- Disruption of mitochondrial function
- DNA damage leading to increased p53 Ser-15 phosphorylation
- Increased CASP3, 8 and 9 activity

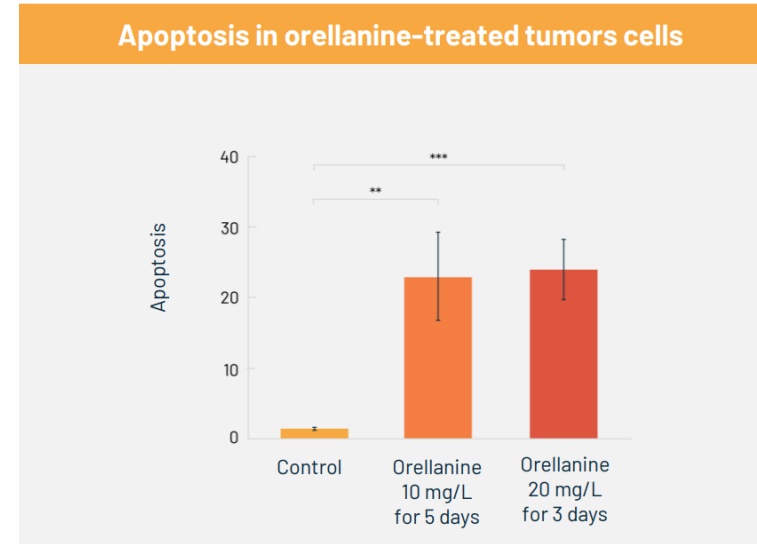
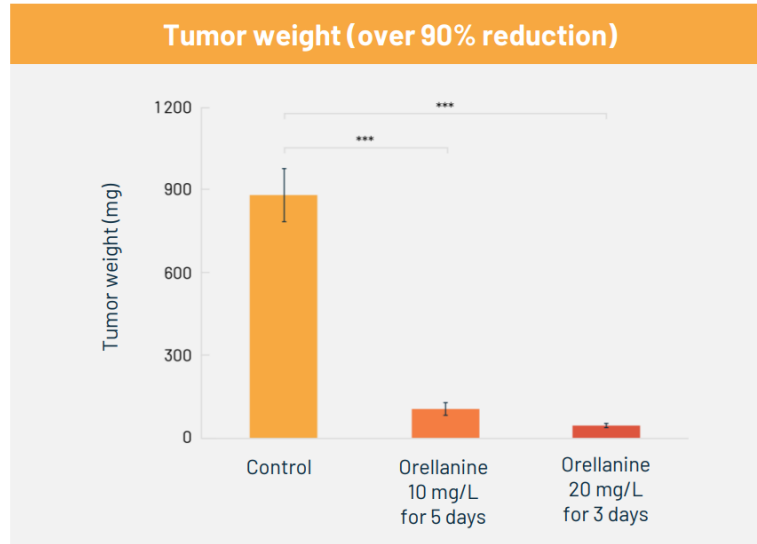
Induction of cell death pathway

CASP, caspase; ROS, reactive oxygen species; SLC, soluble carrier.

Adapted from: Buval, L., et al. (2017). *Oncotarget*, 8(53), 91085-91098 and Nilsson, U. A., et al. (2008). *Free Radic Biol Med*, 44(8), 1562-1569.

Orellanine (ONC175)

PRECLINICAL DATA SHOW ANTI-TUMOR EFFECT BY ORELLANINE



- 3-5 days of orellanine therapy (10-30 μ M) reduced the weight of the human renal cancer tumors and triggered apoptosis in a xenograft rat model of human metastatic renal cancer
- Supports a prolonged exposure time with a lower dose to achieve effect while maintaining a risk/benefit balance

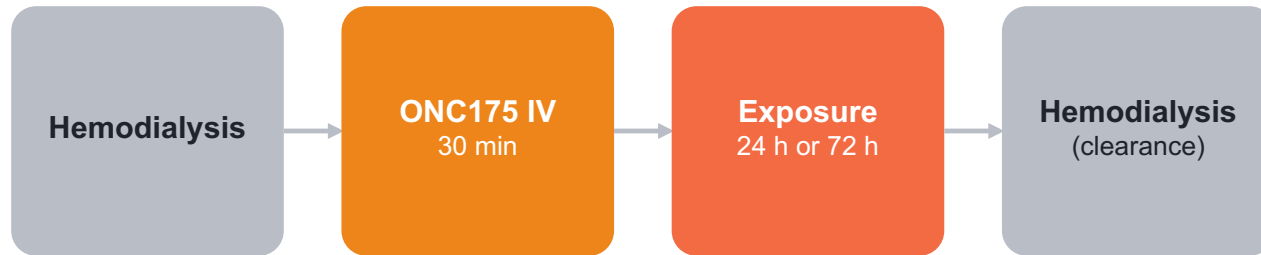
**P<0.01.

***P<0.001.

Buvall, L., et al. (2017). *Oncotarget*, 8(53), 91085-91098

Orellanine (ONC175): organ-directed chemotherapy in ccRCC and papillary RCC on dialysis

ADMINISTRATION SCHEDULE (PART B · 28-DAY CYCLES)



Rationale: orellanine, a toxin from Cortinarius mushrooms, is selective for the proximal tubule, the cell of origin of ccRCC.

Population: metastatic disease on dialysis for renal failure: nephrotoxicity is no longer limiting.

75

Planned patients

Aug 2023

First patient (Karolinska)

Open at H120

Key messages

1

HIF-2 α now behaves like a kinase

Gatekeeper resistance (EPAS1 G323E) and the ferroptosis paradox: the axis we block is also a vulnerability.

2

Biomarker selection is critical

No responses with ALLO-316 below 50% CD70 expression; KIM-1 in plasma identifies who relapses.

3

Engineering expands the target space

L T-cell engagers (XmAb819) and degraders (BMS-986506).

4

ccRCC is not all of kidney cancer

TROP-2 and CDH6 in papillary and clear cell disease, plus theranostic CAIX, open histology- and imaging-specific strategies.



Thank you!