Cáncer Renal ASCO 2026
Ha sido un gran año?.....

Spoiler: NO

Dr Pablo Maroto
Hospital de Sant Pau

Lo más destacado….

A phase II randomized trial of radium-223 and cabozantinib in patients with renal cell carcinoma with bone metastases. RADICAL (Alliance A=31801). *McKay RR et al*

A prospective, multicenter, phase Ib/II trial of first line cadonilimab plus axitinib in advanced non-clear cell renal cell carcinoma. *Hu X et al.*

ctDNA analysis in patients with renal cell carcinoma treated with adjuvant pembrolizumab or placebo in the Keynote 564 trial. *Choueiri TK et al.*

Mensajes

A phase II randomized trial of radium-223 and cabozantinib in patients with renal cell carcinoma with bone metastases. RADICAL (Alliance A=31801). *McKay RR et al*

Randomized academic trials can be completed

A prospective, multicenter, phase Ib/II trial of first line cadonilimab plus axitinib in advanced non-clear cell renal cell carcinoma. *Hu X et al.*

CPI+TKI also works in non clear cell carcinoma

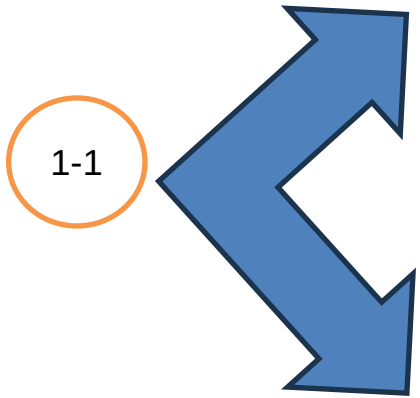
ctDNA analysis in patients with renal cell carcinoma treated with adjuvant pembrolizumab or placebo in the Keynote 564 trial. *Choueiri TK et al.*

ctDNA may offer an opportunity for escalation or de-escalation

RADICAL

Incremento a 60 mg +28 días si no contraindicación

Any histology RCC
1 or more untreated BM
KPS >50%
OTT use unless contraindicated
Opioids allowed
Excluded: Impending fractures or cord compression



Cabozantinib 40-60 mg/day + Radium-223 55 kBq/Kg iv./28 d x 6

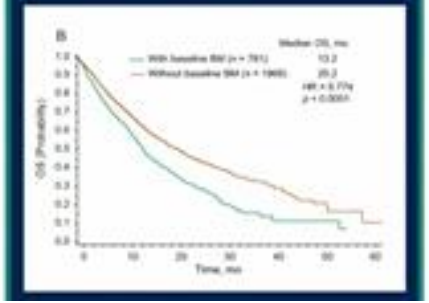
Cabozantinib 60 mg/day

1º Endpoint: SSE-FS
2º Endpoint:
Safety, SSE-FS in subsets, time to first SSE, ORR, PFS, time to subsequent treatment, OS

Stratification Factors:
Prior/concurrent OTT use
IMDC risk group
Prior treatment
Opioid use

BM in RCC

BM occur in 30% of patients with RCC and are associated with worse OS and QOL

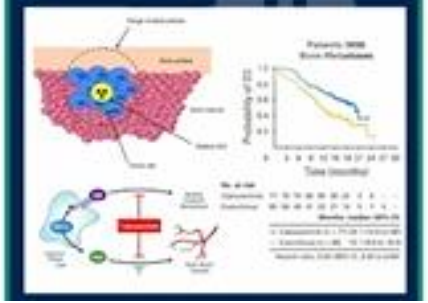


BM Pathophysiology

Dysregulated osteoblast/osteoclast activity in the bone microenvironment

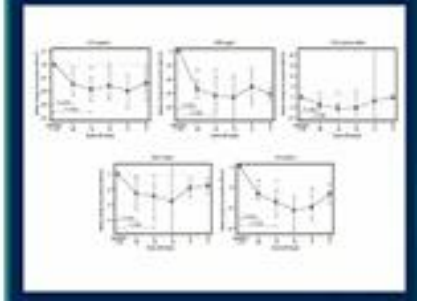
Therapeutic Rationale

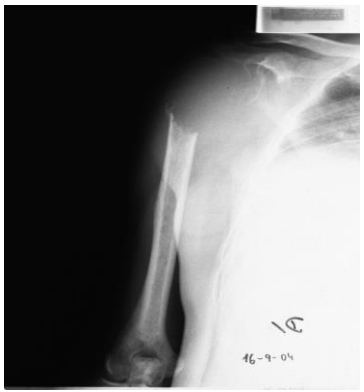
Radium-223 (bone-seeking α-emitter) + cabozantinib (an active SOC in RCC)

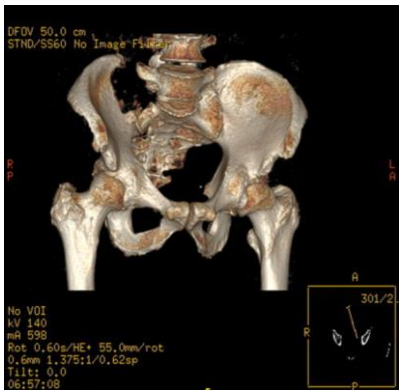


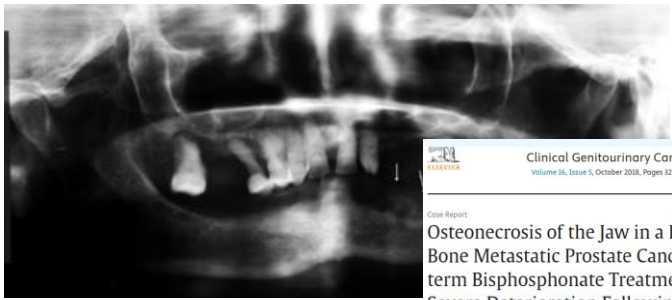
Pilot Study

Pilot study of radium-223 + VEGF-TT (N=30) showed safety and drop in bone markers





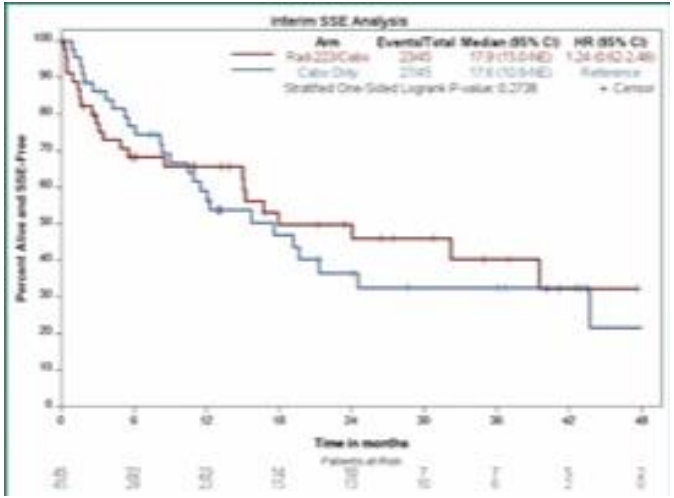




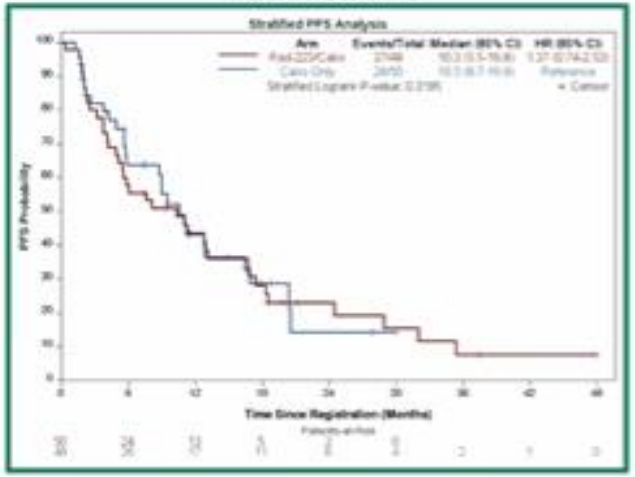
Clinical Genitourinary Cancer
Volume 16, Issue 5, October 2018, Pages 328-331

Case Report

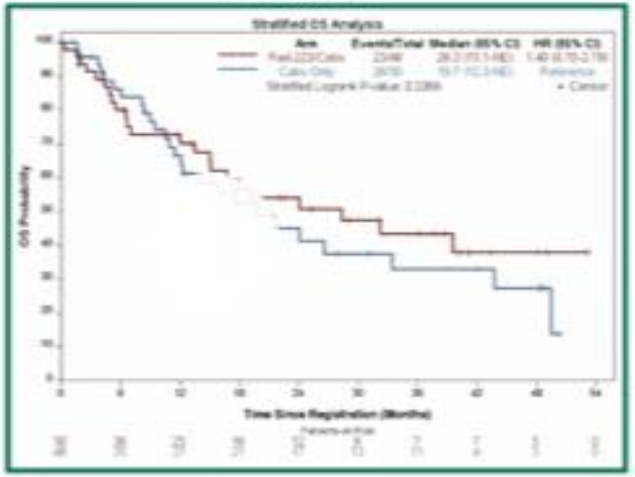
Osteonecrosis of the Jaw in a Patient With Bone Metastatic Prostate Cancer After Long-term Bisphosphonate Treatment With Severe Deterioration Following Radium-223



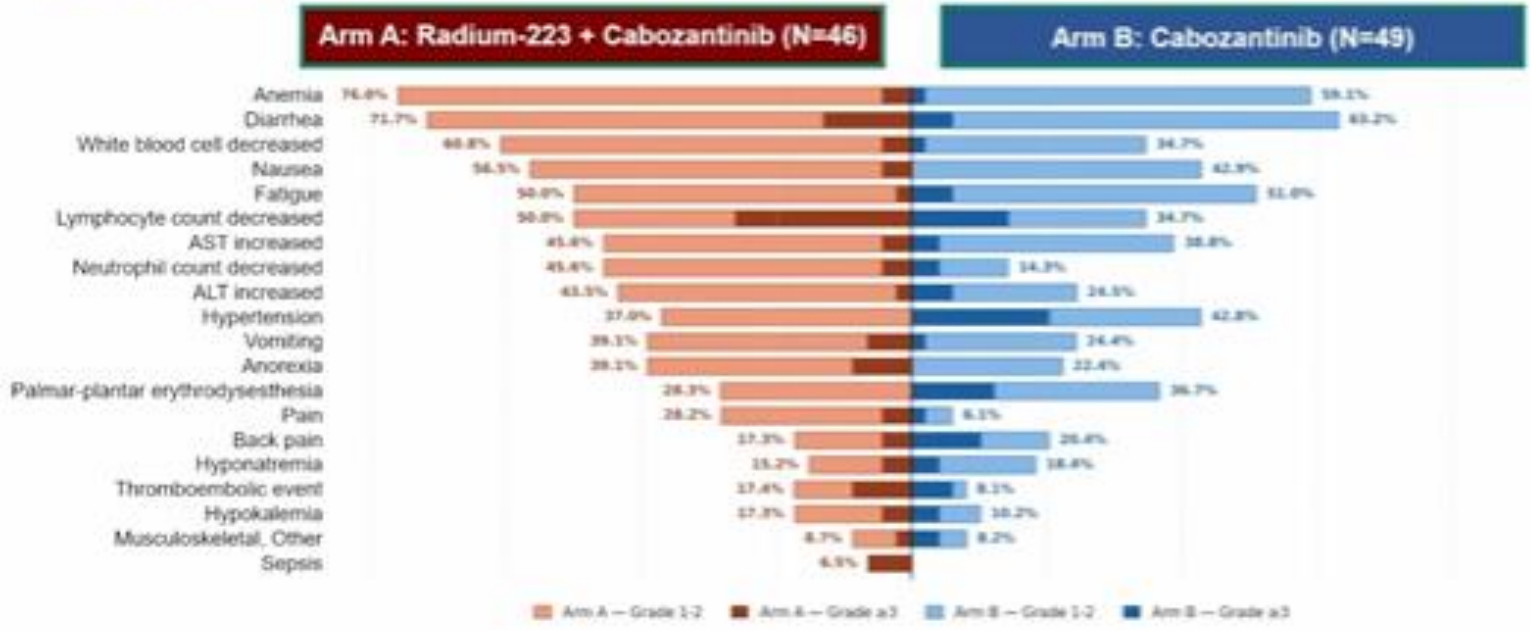
Stratified PFS



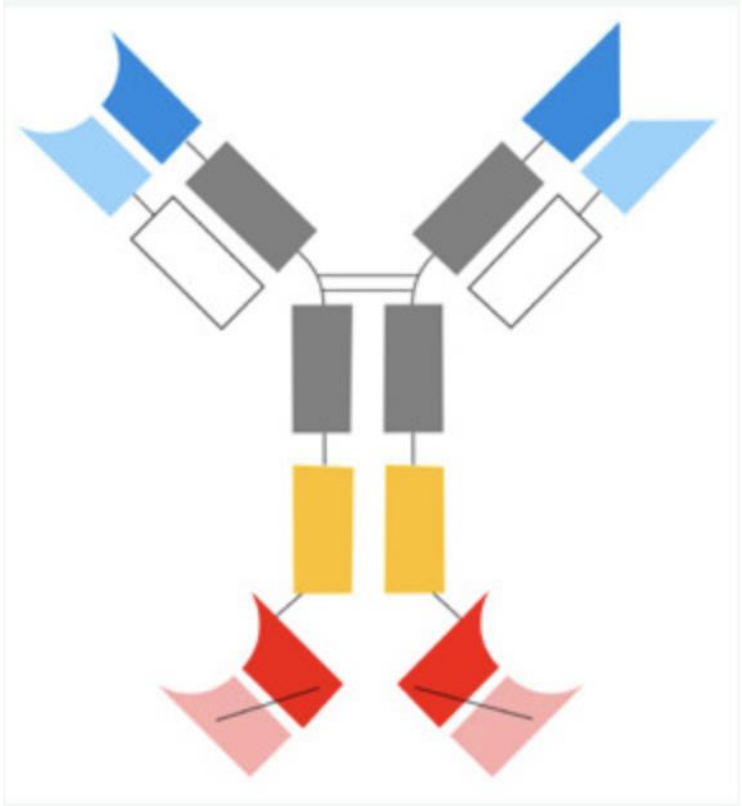
Stratified OS



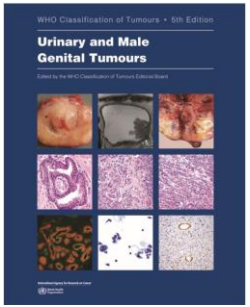
Received Therapy – Safety Analysis (≥3% Grade ≥3) (N=95)



Cadonilimab. Actividad en carcinoma no células claras + Axitinib



Background: non-clear cell RCC



WHO 2004

Clear cell renal cell carcinoma
Multi-locular clear cell renal cell carcinoma
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
Xp11 translocation carcinoma
Carcinoma associated with neuroblastoma
Mucinous, tubular, and spindle cell carcinoma
Renal cell carcinoma, unclassified
Papillary adenoma
Oncocytoma

WHO 2016

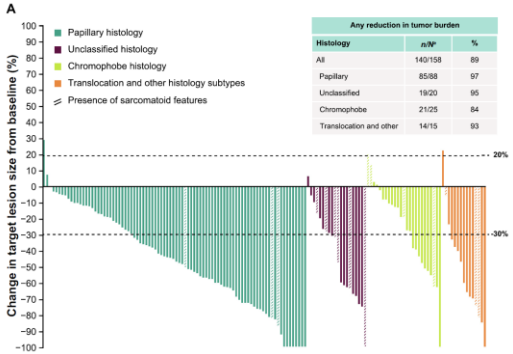
Clear cell renal cell carcinoma
Multilocular cystic renal neoplasm of LMP
Papillary renal cell carcinoma
Hereditary leiomyomatosis and RCC associated
Chromophobe renal cell carcinoma
Collecting duct carcinoma of the kidney
Renal medullary carcinoma
MiT Family translocation carcinomas
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease associated renal cell carcinoma
Clear cell papillary renal cell carcinoma
Succinate dehydrogenase (SDH) deficient renal carcinoma
Renal cell carcinoma, unclassified

WHO 2022

Clear cell
Multilocular cystic renal neoplasm of low m.p
ELOC Mutation
Papillary RCC
Fumarate H deficient
Mucinous tubular spindle RCC
Tubulocystic
Clear cell papillary RC tumor
Chromophobe
Oncocytoma
SDH deficient
Other oncocytic tumours
TFE3- rearranged
TFEB- altered
Collecting duct carcinoma
***SMARCB1* deficient renal medullary carcinoma**
***ALK* rearranged renal cell carcinomas**
Eosinophilic solid and cystic RCC
Acquired cystic disease associatedRCC
RCC NOS

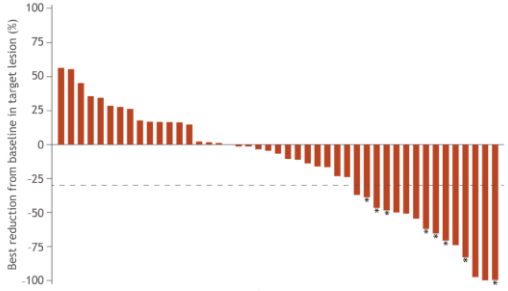
Background: Contemporary Regimen in ncRCC

B61: Lenvatinib + Pembrolizumab

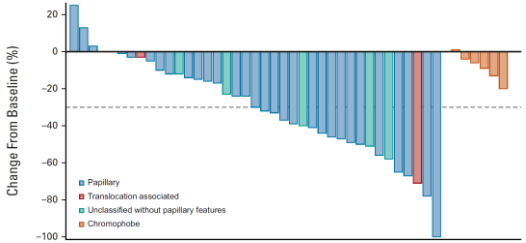


Any reduction in tumor burden		
Histology	n/N*	%
All	140/158	89
Papillary	85/88	97
Unclassified	19/20	95
Chromophobe	21/25	84
Translocation and other	14/15	93

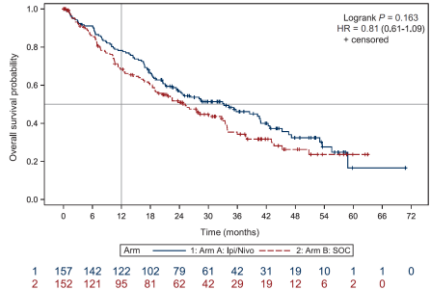
CM920: Ipilimumab/Nivolumab



MSK IIT: Cabozantinib + nivolumab



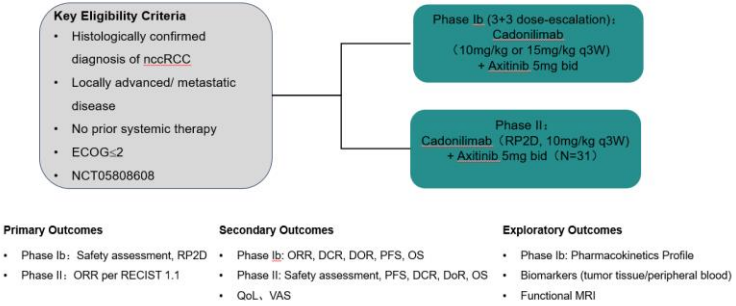
SUNNIFORECAST: Ipilimumab + Nivolumab vs SOC



Voss MH et al., *Eur Uro* 2025
Fitzgerald K et al., *Eur Uro* 2024
Tykodi S et al., *JITC* 2022
Bergmann L et al., *Ann Oncol* 2025

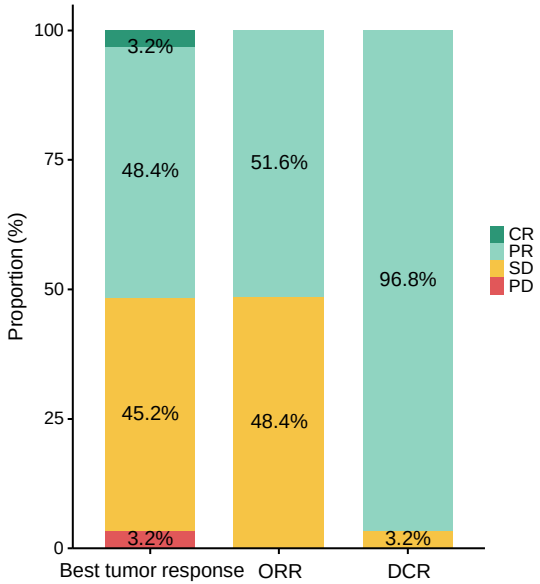
Patients enrolled: ncRCC variants

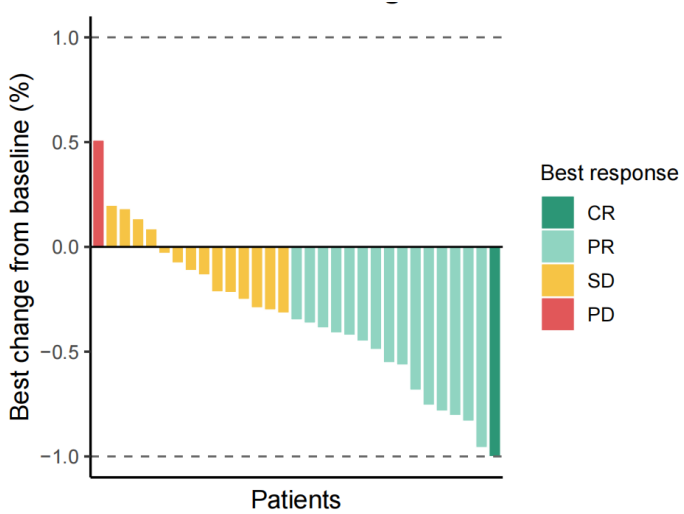
Study Design



	Phase IB (N = 6)	Phase II (N = 31)	FAS (N = 37)
Histopathological type (After genetic testing), n(%)			
FH-dRCC	5 (83)	11 (35)	16 (43)
TFE3-rRCC	1 (17)	8 (26)	9 (24)
TFEB-altered RCC	0 (0)	3 (10)	3 (8)
SMARCB1-dRMC	0 (0)	2 (6)	2 (5)
Collecting duct carcinoma	0 (0)	2 (6)	2 (5)
chRCC	0 (0)	2 (6)	2 (5)
uRCC / RCC, NOS	0 (0)	3 (10)	3 (8)

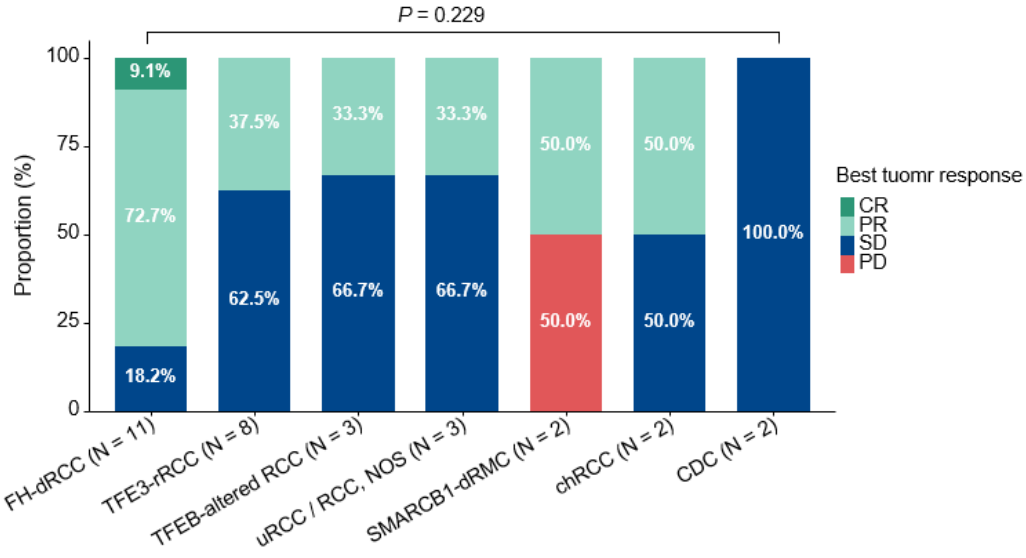
Primary Endpoint Phase 2: ORR by RECIST 1.1





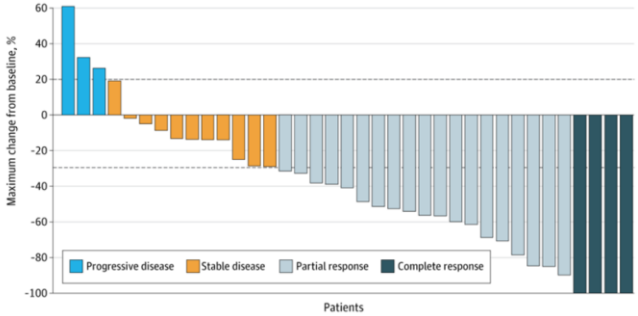
- **Median time to response (range)** = 3.5 (2.7, 9.5) months
- **Median duration of response (95%CI)** = 17.5 (11.2, NR) months

Efficacy across histologies



Hu X et al., ASCO 2026

Phase II sintilimab + axitinib in FHd RCC



Zhang X et al., *Jama Oncol* 2025

Final Results of a Phase 2 Trial of Cabozantinib plus Nivolumab (CaboNivo) in Patients with Non-Clear Cell Renal Cell Carcinoma (nccRCC)

Darren R. Feldman, MD

With additional patients and longer follow-up (~50 months), final results reaffirm antitumor efficacy for cabozantinib plus nivolumab in both previously treated and treatment-naïve non-clear cell RCC

Responses were observed across non-clear cell RCC histologies except chromophobe RCC, including in 7 of 8 patients with FH-deficient RCC

The high response rate and safety profile supports cabozantinib plus nivolumab as a treatment option for patients with non-clear cell RCC histologies

Efficacy

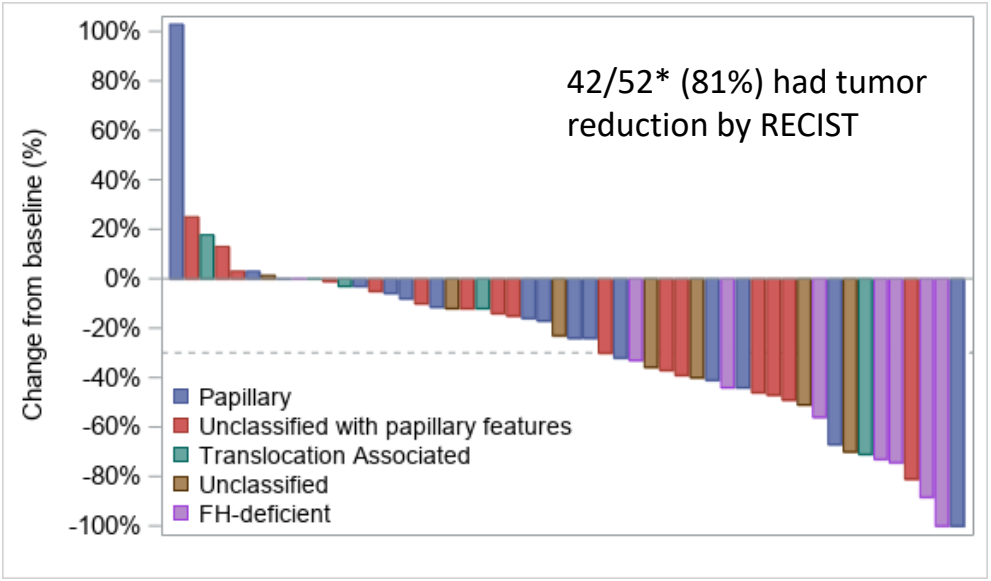
Outcome	All pts (n=53)	1st line (n=39)	2nd line (n=14)	Papillary (n=16)	UCPF (n=16)	FH-def** (n=8)	Unclass. (n=8)	Transloc. (n=5)
PR/CR, n (%)	23 (43)*	18 (46)*	5 (36)	5 (31)*	13 (38)	7 (88)	4 (50)	1 (20)
SD, n (%)	27 (51)	19 (49)	8 (57)	10 (63)	10 (62)	1 (12)	2 (25)	4 (80)
PD, n (%)	3 (6)	2 (5)	1 (7)	1 (6)	0	0	2 (25)	0
mPFS, mo. (95% CI)	11 (8-14)	11 (8-16)	14 (5-23)	11 (7-25)	10 (5-13)	16 (5-37)	8 (1-34)	14 (5-41)

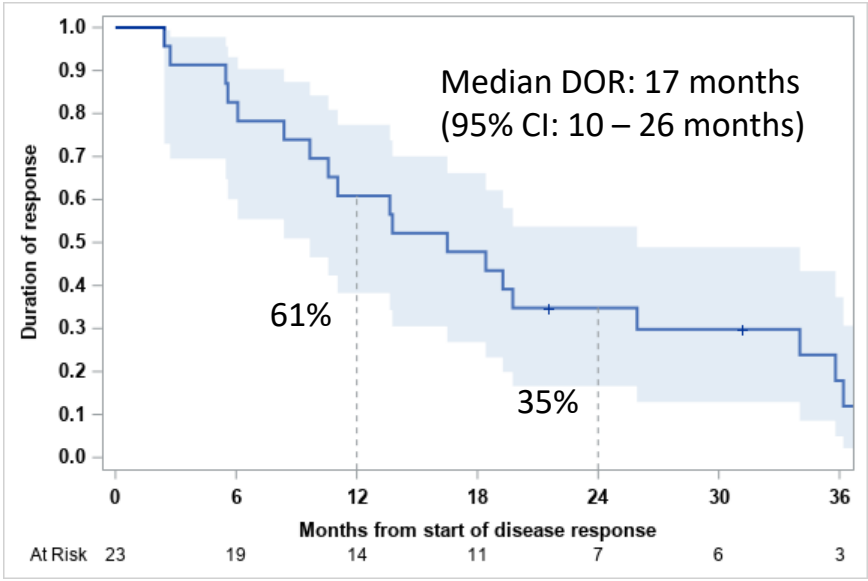
*1 patient with papillary RCC treated in 1st-line achieved a CR; all other responses were PRs
**FH-deficient RCC previously included primarily in papillary cohort in prior presentations/manuscripts[1,2]

Abbreviations: FH-def, Fumarate Hydratase deficient; mPFS, median PFS; Transloc., translocation-associated RCC; Unclass., unclassified; UCPF, unclassified with papillary features

[1]Lee JCO 2022
[2]Fitzgerald Eur Urol 2024

Results


Change from baseline (%)
100%
80%
60%
40%
20%
0%
-20%
-40%
-60%
-80%
-100%
42/52* (81%) had tumor reduction by RECIST
Papillary
Unclassified with papillary features
Translocation Associated
Unclassified
FH-deficient


Duration of response
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Median DOR: 17 months
(95% CI: 10 – 26 months)
61%
35%
0
6
12
18
24
30
36
Months from start of disease response
At Risk 23 19 14 11 7 6 3

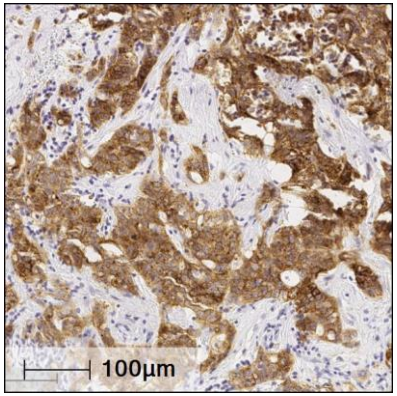
Prospective clinical activity and preclinical basis of panitumumab-based EGFR blockade in SMARCB1-deficient renal medullary carcinoma (RMC): a collaborative multi-institutional study

Pavlos Msaouel[1], Eric S. Rupe[1], Xinyue Chen[1], Ritesh R. Kotecha[2], Damian T. Rieke[3], Bradley A. McGregor[4], Najat C. Daw[1], Alice C. Fan[5], Eric M. Knoche[6], Christos E Kyriakopoulos[7], Aly-Khan A. Lalani[8], Amartej Merla[9], Martin H. Voss[2], Neil M. Reaume[10], Alexander J. Lazar[1], Luisa M. Solis Soto[1], Bora Lim[1], Nizar M. Tannir[1], Menuka Karki[1], Niki M. Zacharias[1]

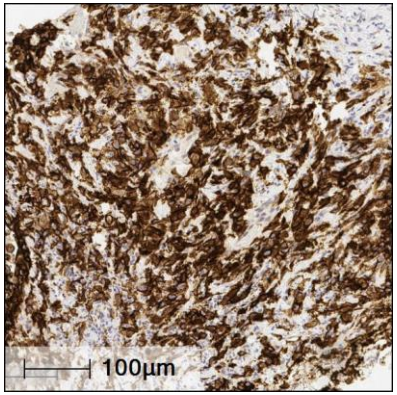
[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[2]Memorial Sloan Kettering Cancer Center, New York, NY, USA
[3]Charité - Universitätsmedizin Berlin, Berlin, Germany
[4]Dana-Farber Cancer Institute, Boston, MA, USA
[5]Stanford University School of Medicine, Stanford, CA, USA
[6]Washington University in St Louis School of Medicine, St Louis, MO, USA
[7]University of Wisconsin, Madison, WI, USA
[8]McMaster University, and Juravinski Cancer Centre, Hamilton, Ontario, Canada.
[9]City of Hope, Duarte, CA, USA.
[10]The Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, ON, Canada.

EGFR upregulation in RMC

EGFR IHC moderate (2+)

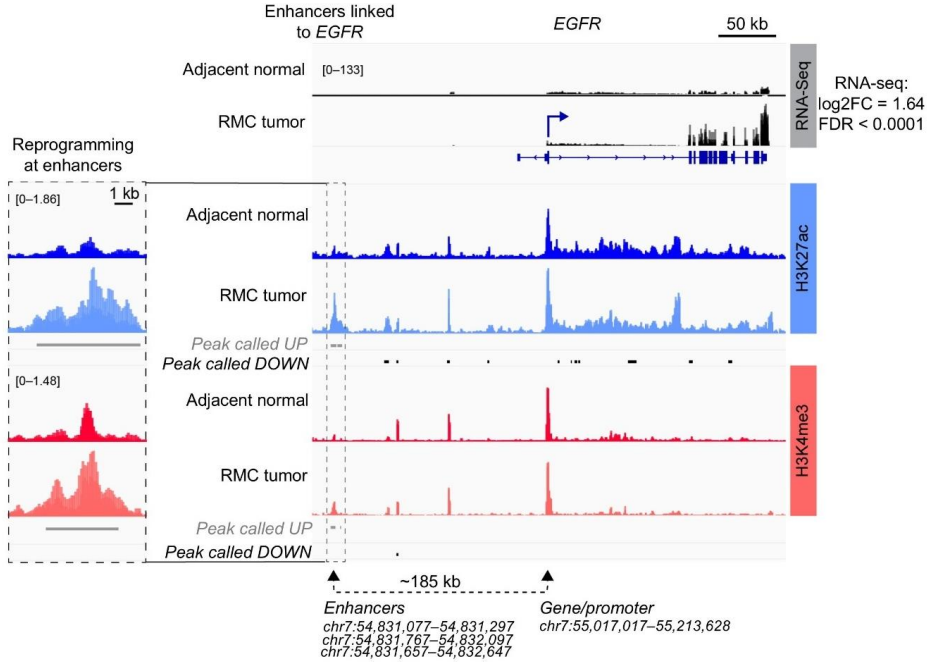


EGFR IHC moderate (3+)



EGFR intensity by IHC

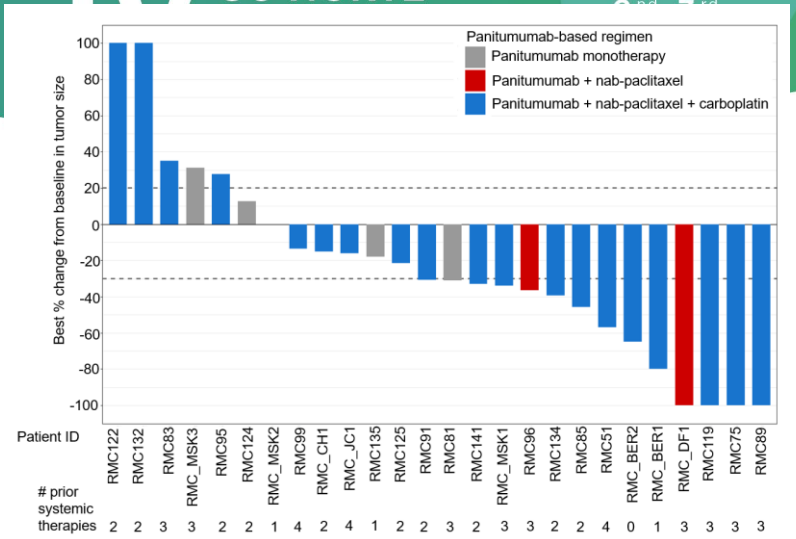
	Negative (0)	Weak (1+)	Moderate (2+)	Strong (3+)
Number of RMC samples, n (%)	0/11 (0%)	0/11 (0%)	3/11 (27.3%)	8/11 (72.7%)

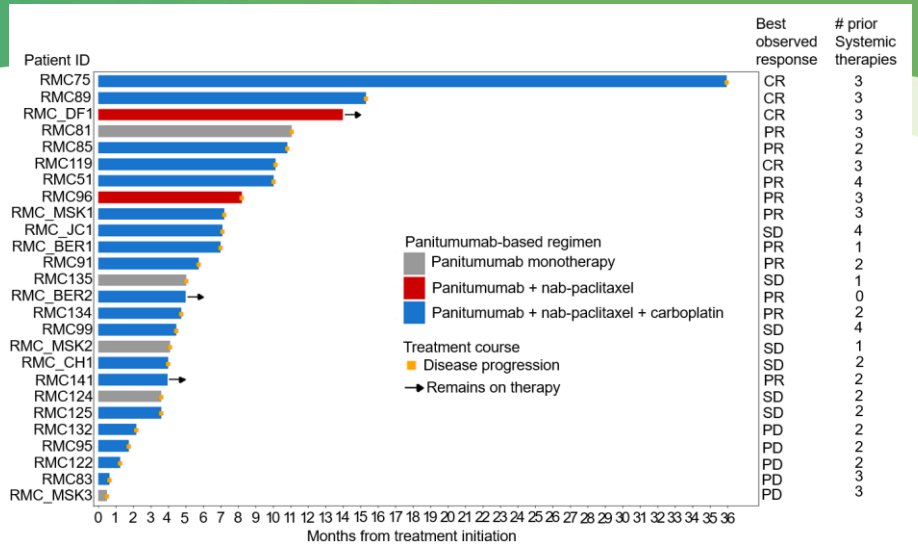


EGFR-linked enhancer region **EGFR-active transcriptional state**

[1]Zacharias NM, et al. *(In revision)*
[2]Msaouel P, et al. *Cancer Cell*. 2020; PMID: 32359397
[3]Msaouel P, et al. *Cell Rep Med*. 2025; PMID: 41172996

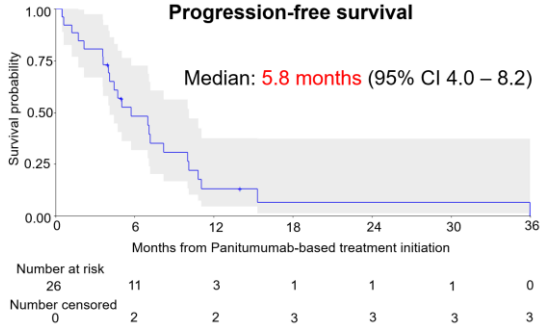
Prospective Multi-National Registry Results

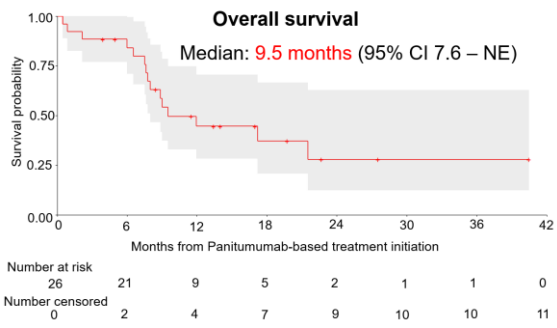




ORR 53.9% (14/26)

	Total (N=26)
Best overall response, n (%)	
Complete response	4 (15.4%)
Partial response	10 (38.5%)
Stable disease	7 (26.9%)
Progressive disease	5 (19.2%)
Depth of response %	
Median (IQR)	-30.9 (-58.9, +3.1)





[1]Zacharias NM, et al. *(In revision)*

ctDNA en participantes con RCC en KEYNOTE-564.

Key Takeaways

Exome-based ctDNA positivity at baseline was associated with worse DFS to both adjuvant pembrolizumab and placebo

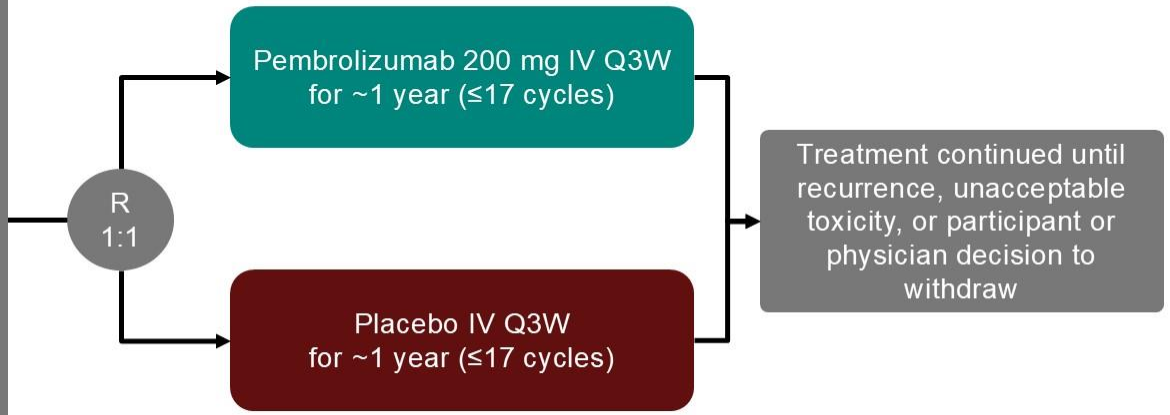
Baseline ctDNA positivity rate was 5.4% to 8.2%, with higher positivity detected using higher variant numbers

Specificity of baseline ctDNA for recurrence was 96% to 99%, and sensitivity for recurrence was 10% to 15%

KEYNOTE-564 Study Design (NCT03142334)

Key Eligibility Criteria
- Age ≥18 years
- Histologically confirmed clear cell RCC
- No prior systemic therapy for advanced disease
- Surgery ≤12 weeks prior to randomization
- Postnephrectomy intermediate-high risk of recurrence (M0):
  - pT2, grade 4 or sarcomatoid, N0
  - pT3, any grade, N0
- Postnephrectomy high risk of recurrence (M0):
  - pT4, any grade, N0
  - Any pT, any grade, N+
- Postnephrectomy and complete resection of metastasis (M1 NED)
- ECOG PS score of 0 or 1

Stratification Factors
- M stage (M0 vs M1 NED)
- M0 group further stratified:
  - ECOG PS score of 0 vs 1
  - US vs rest of the world

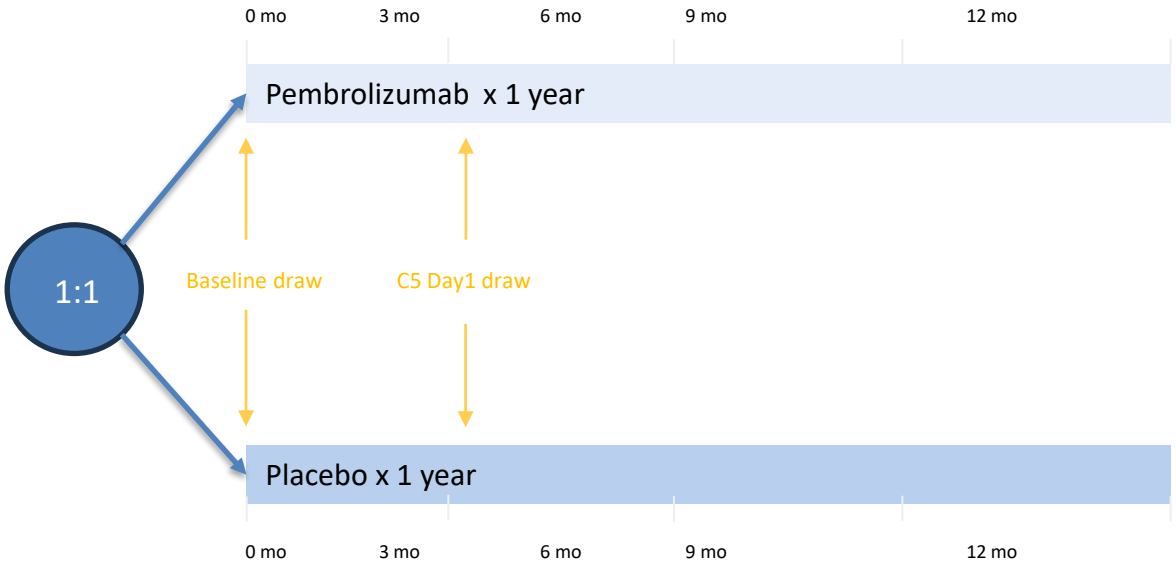


Primary end point: DFS by investigator
Key secondary end point: OS
Other secondary end point: Safety

Exploratory end points: Association of baseline ctDNA metrics and ctDNA change from baseline to cycle 5 day 1 (C5D1) with DFS[a] for pembrolizumab and placebo separately, and ctDNA clearance rate at C5D1

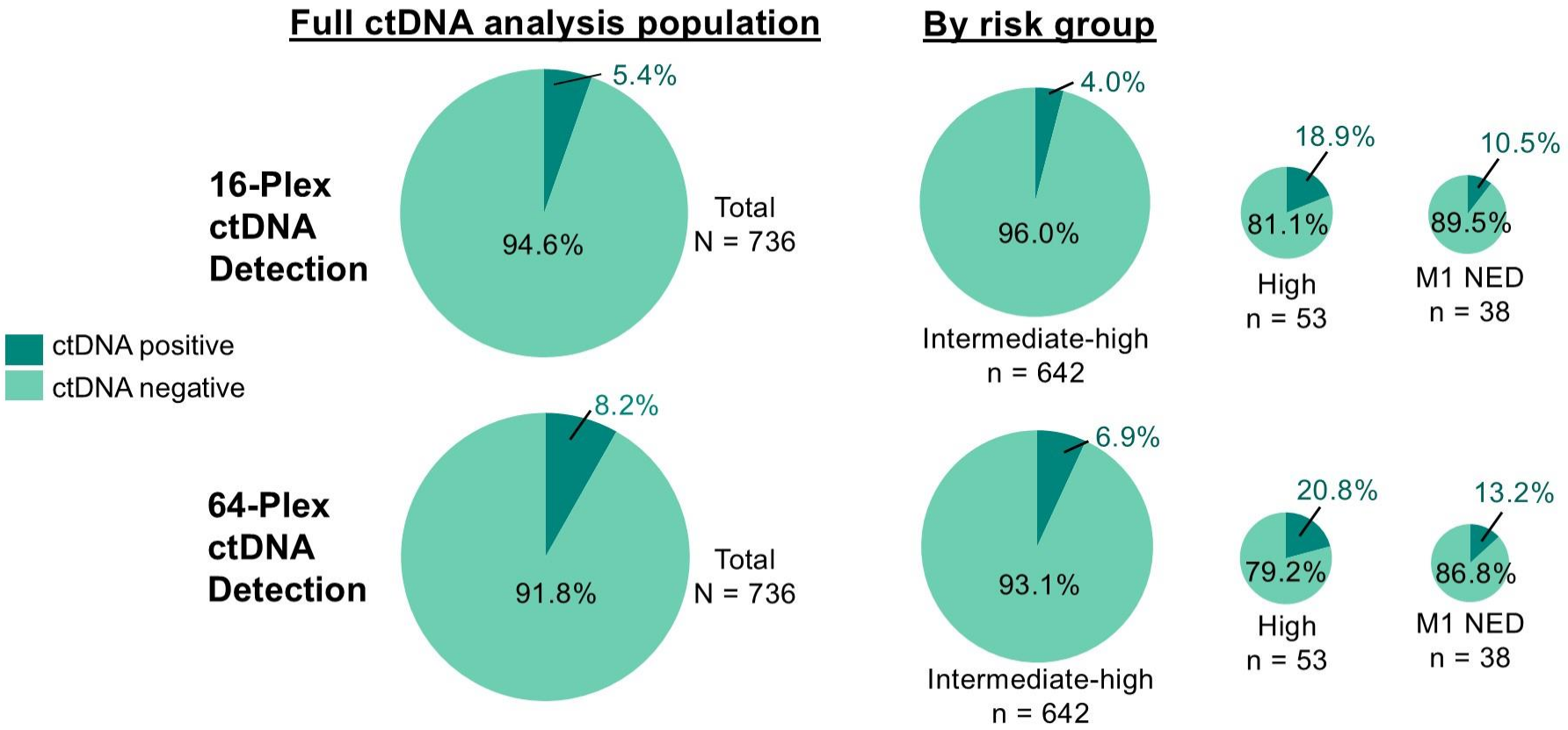
[a]Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of baseline ctDNA to predict disease recurrence were also evaluated.

Methodology: Two timepoints / exploratory endpoints



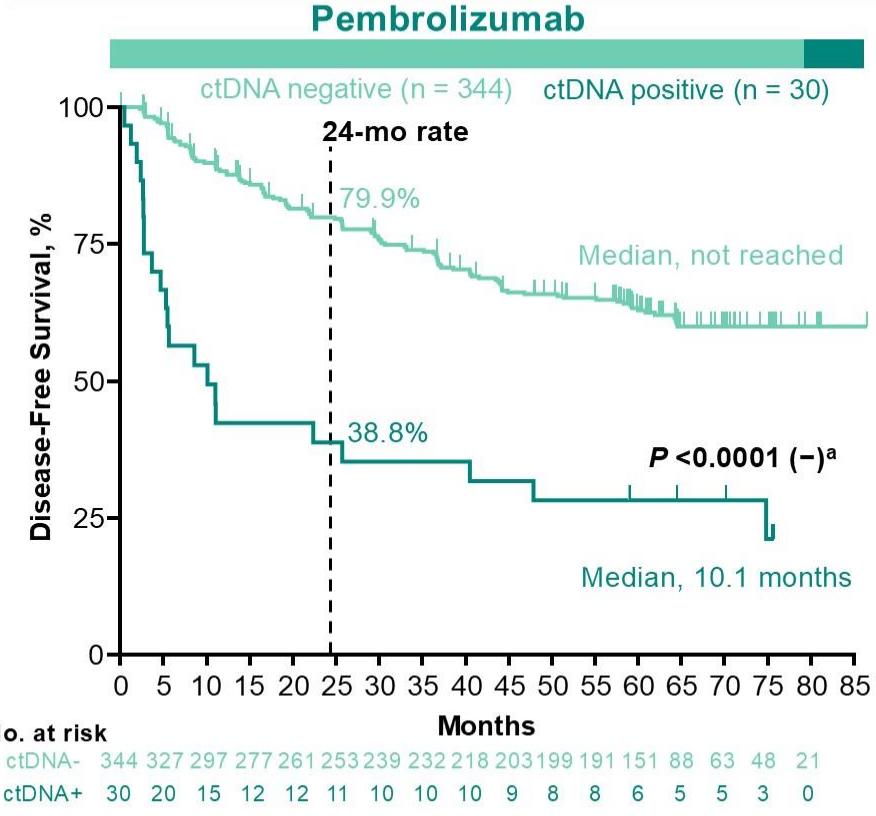
Exploratory end points: Association of baseline ctDNA metrics and ctDNA change from baseline to cycle 5 day 1 (C5D1) with DFS[a] for pembrolizumab and placebo separately, and
ctDNA clearance rate at C5D1

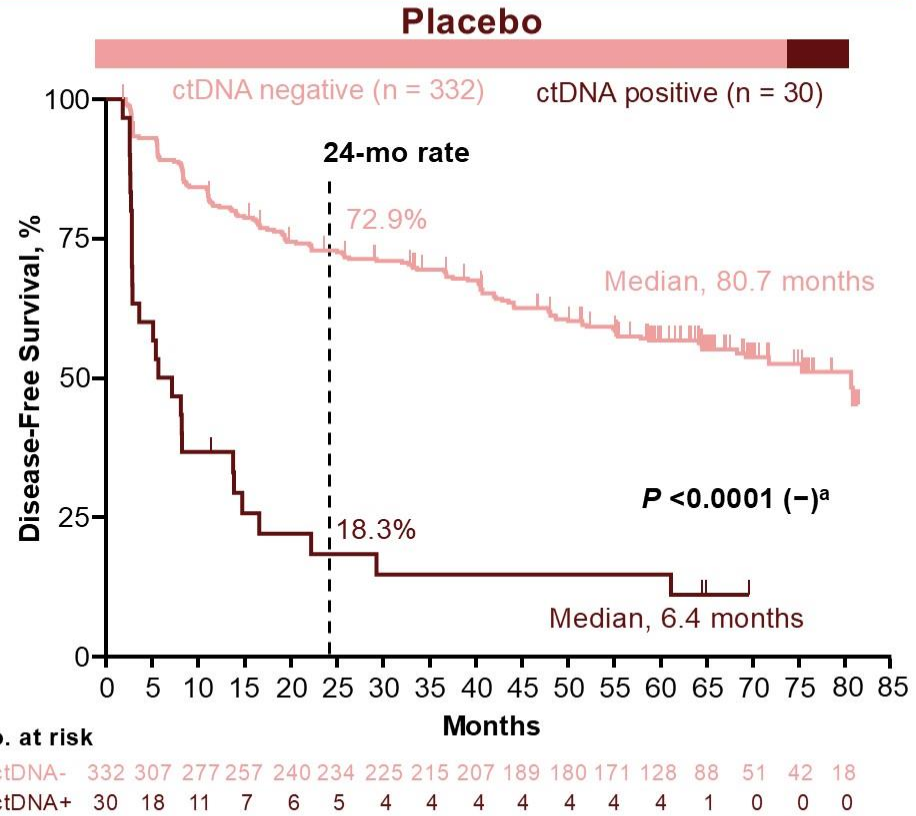
Exome-based ctDNA Status at Baseline Postsurgery[a]



[a]Analysis includes both treatment arms. Clinical data cutoff: September 25, 2024.

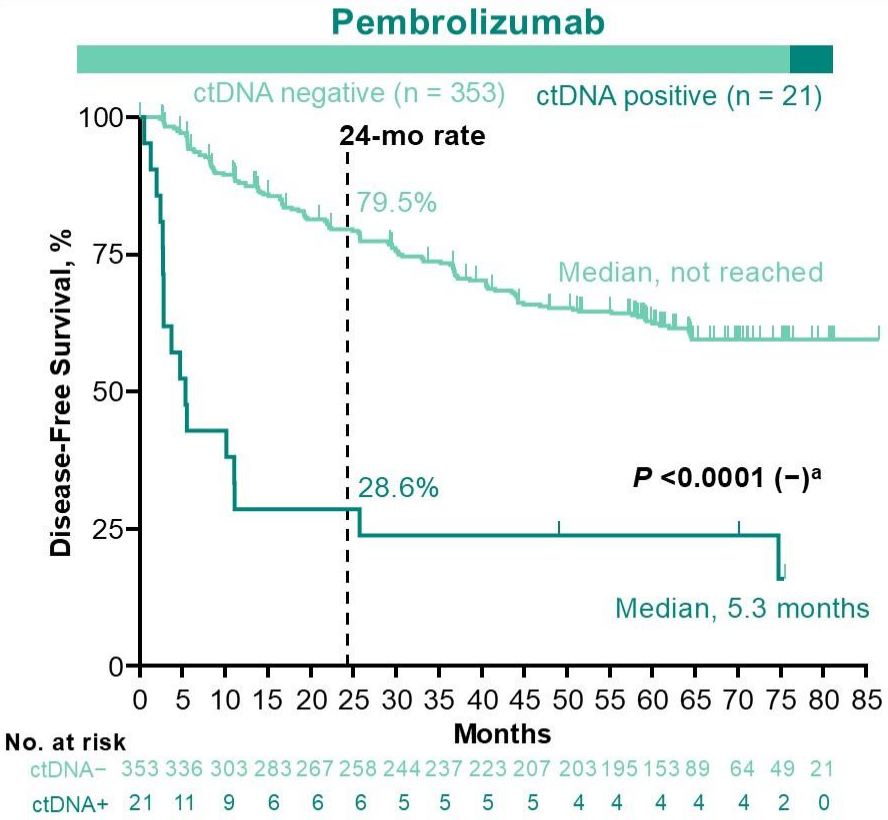
Kaplan-Meier Estimates of DFS by Baseline ctDNA Status Within Each Treatment Arm: Exome-Based 64-Plex Assay

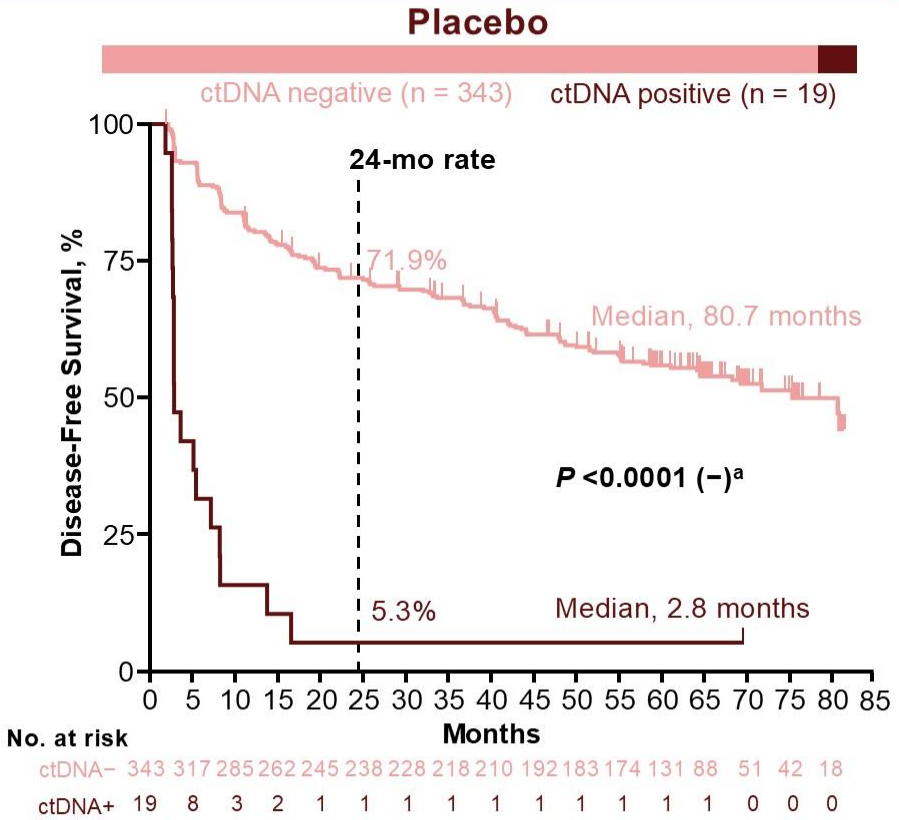




[a]"–" indicates that the observed association is negative. The association between baseline ctDNA metrics and DFS remained significant after adjusting for risk groups and other stratification factors. Statistical significance prespecified at multiplicity-adjusted α = 0.05. Clinical data cutoff: September 25, 2024.

Kaplan-Meier Estimates of DFS by Baseline ctDNA Status Within Each Treatment Arm: Exome-Based 16-Plex Assay





[a]"–" indicates that the observed association is negative. The association between baseline ctDNA metrics and DFS remained significant after adjusting for risk groups and other stratification factors. Statistical significance prespecified at multiplicity-adjusted α = 0.05. Clinical data cutoff: September 25, 2024.

Specificity, Sensitivity, PPV, and NPV of Baseline ctDNA to Predict Disease Recurrence

Exome-based 16-Plex

Placebo

	DFS event	No DFS event	
ctDNA positive	18	1	**PPV 95%**
ctDNA negative	155	188	**NPV 55%**
	Sensitivity 10%	**Specificity 99%**	

Pembrolizumab

	DFS event	No DFS event	
ctDNA positive	17	4	**PPV 81%**
ctDNA negative	129	224	**NPV 63%**
	Sensitivity 12%	**Specificity 98%**	

Exome-based 64-Plex

Placebo

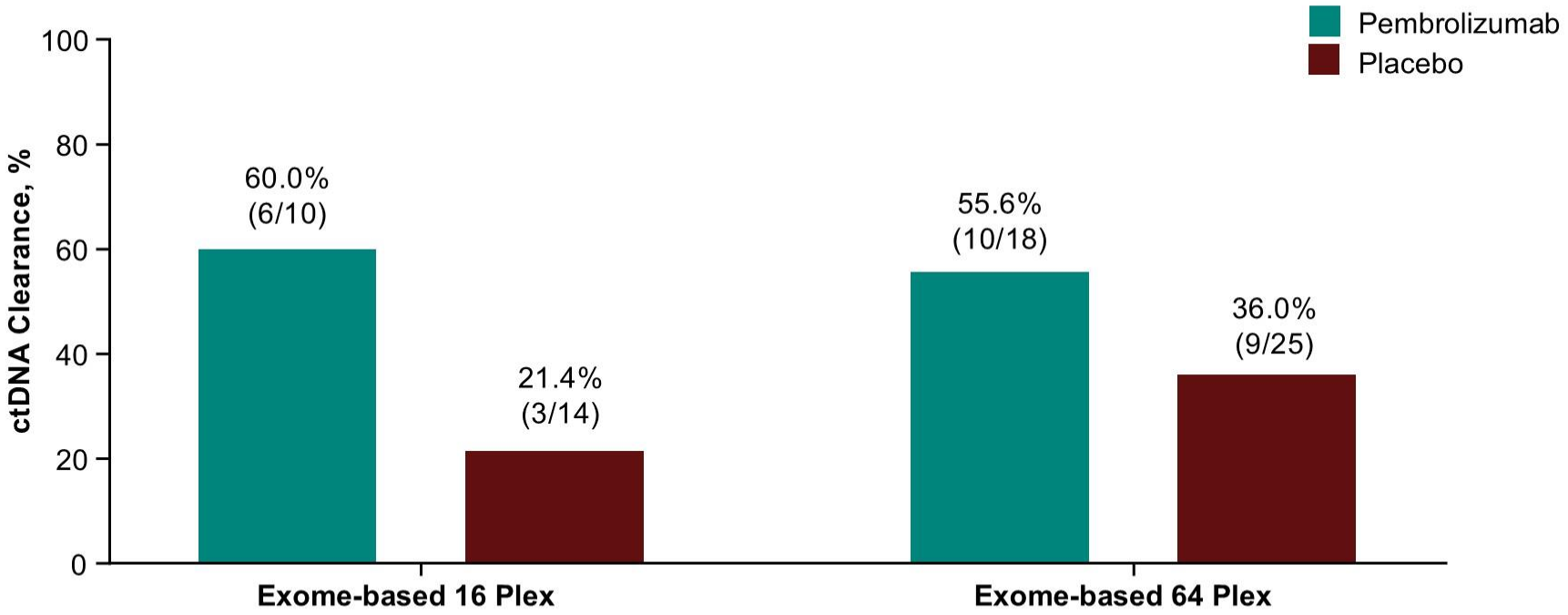
	DFS event	No DFS event	
ctDNA positive	26	4	**PPV 87%**
ctDNA negative	147	185	**NPV 56%**
	Sensitivity 15%	**Specificity 98%**	

Pembrolizumab

	DFS event	No DFS event	
ctDNA positive	22	8	**PPV 73%**
ctDNA negative	124	220	**NPV 64%**
	Sensitivity 15%	**Specificity 96%**	

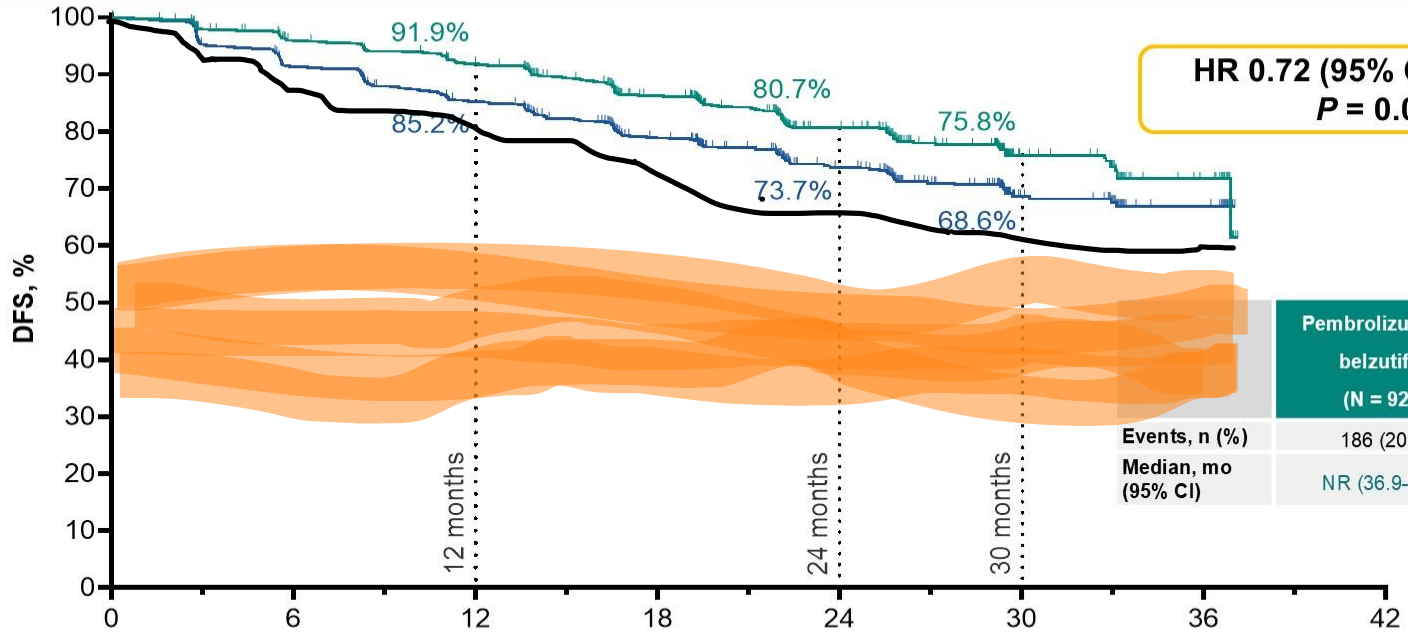
Sensitivity is the percentage of ctDNA-positive participants among all participants with a DFS event. Specificity is the percentage of ctDNA-negative participants among all participants without a DFS event. PPV is the probability of a DFS event given sample-level positive status. NPV is the probability of no DFS event given sample-level negative status. Clinical data cutoff: September 25, 2024.

ctDNA Clearance Rate at C5D1



ctDNA clearance was defined as the percentage of participants who were ctDNA-negative at C5D1 among those with detectable ctDNA at baseline and evaluable ctDNA at C5D1.
Clinical data cutoff: September 25, 2024.

DFS by Investigator, ITT Population



HR 0.72 (95% CI, 0.59–0.87)
P* = 0.0003

	Pembrolizumab + belzutifan (N = 921)	Pembrolizumab + placebo (N = 920)
Events, n (%)	186 (20.2)	246 (26.7)
Median, mo (95% CI)	NR (36.9–NR)	NR (NR–NR)

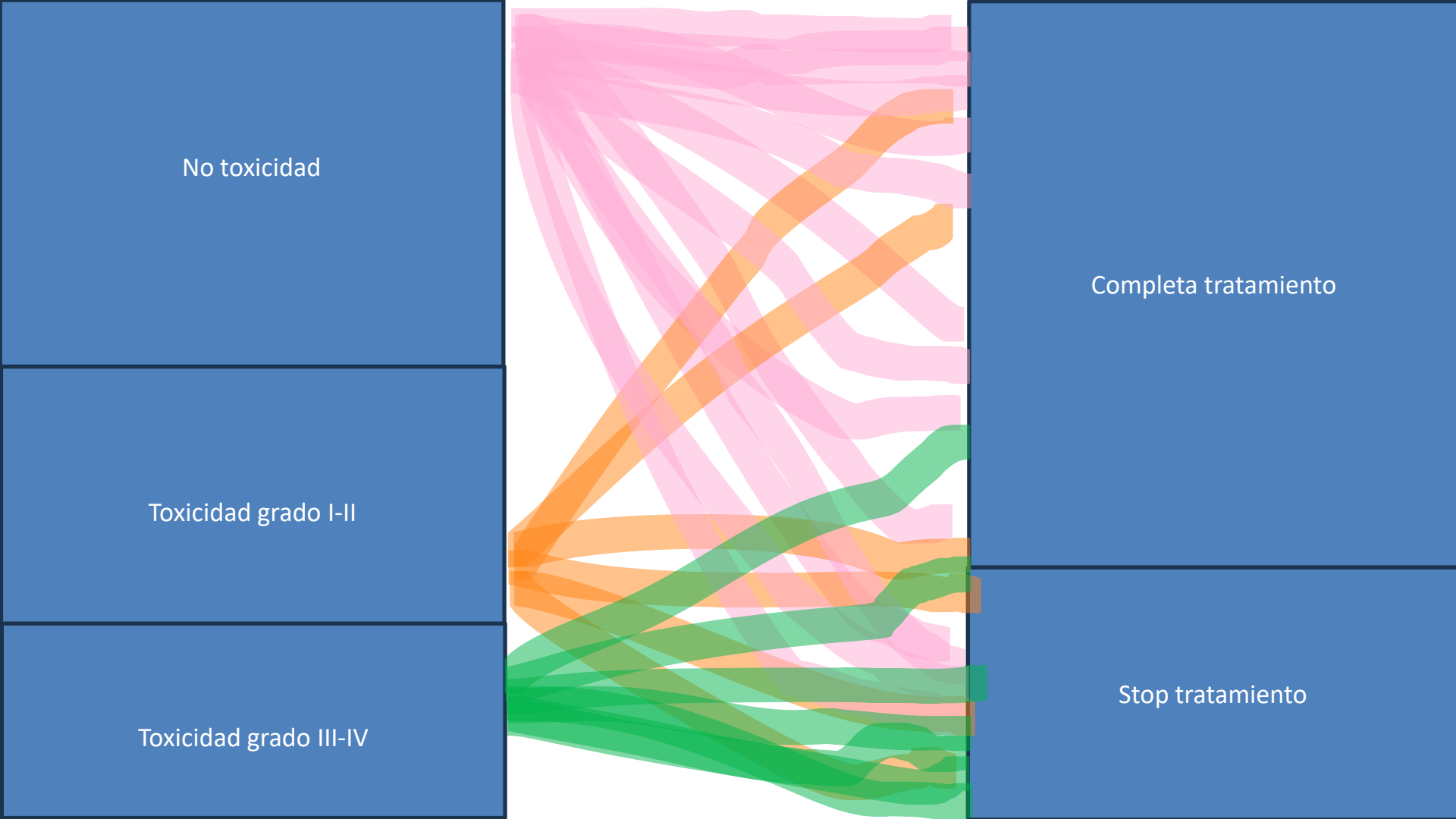
No. at Risk

Pembrolizumab + belzutifan	921	850	805	669	451	153	35	0
Pembrolizumab + placebo	920	823	759	619	417	140	38	0

*Denotes statistical significance by stratified log-rank test (p-value boundary, 0.01632).
NR, not reached. ITT population comprised all randomized participants. HRs and 95% CI estimated via stratified Cox proportional hazard model.

Median follow-up: 28.4 months (range, 15.0–40.1).

Data cutoff: August 23, 2025.


No toxicidad
Toxicidad grado I-II
Toxicidad grado III-IV
Completa tratamiento
Stop tratamiento

Y la, para mí, más sorprendente…..

Microbial dysbiosis as a predictor of benefit from CBM588 as an adjunct to immune checkpoint blockade – based first line therapies in mRCC

Key Takeaway Points

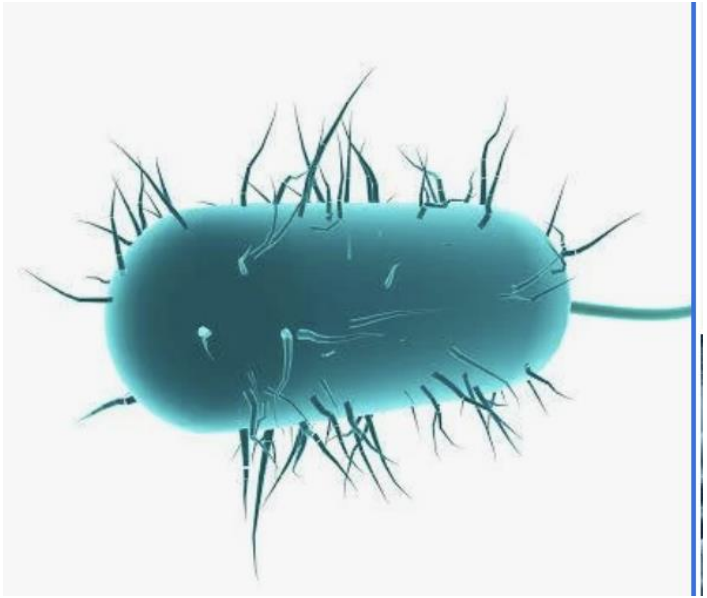
1. **CBM588 showed enhanced clinical activity with first-line ICB for mRCC**
2. **CBM588 with first-line ICB conferred a greater benefit with dysbiotic stool genotypes**
3. **Phase III randomized trial BIOFRONT will further assess clinical activity of CBM588 in mRCC**

Métodos.

- Análisis de resultados de dos ensayos fase I de nivolumab/ipilimumab con o sin **CBM588** (Clostridium butyricum MIYAIRI 588): Una bacteria productora de ácido butírico y esporas, usada como probiótico
- Aplican datos metagenomicos de heces y calculan TOPOSCORE y S-Score microbial dysbiosis como predictors del beneficio de CBM588 como adyuvante a inmunoterapia en primera línea para mRCC
- Analizan SLP y en función del genotipo SIG1+ vs SIG2+ Y S-SCORE

TOPOSCORE (Topological Score) is a diagnostic biomarker that evaluates a patient's **gut microbiome** to predict how well they will respond to **cancer immunotherapies** (such as immune checkpoint inhibitors or CAR T-cell therapy).

Developed by researchers at the Gustave Roussy cancer center, it is highly useful in personalizing cancer treatment.



How it Works

•**Ecological Balance:** It measures the ratio of "favorable" (anti-inflammatory) to "unfavorable" (pro-inflammatory) bacterial communities in your gut.

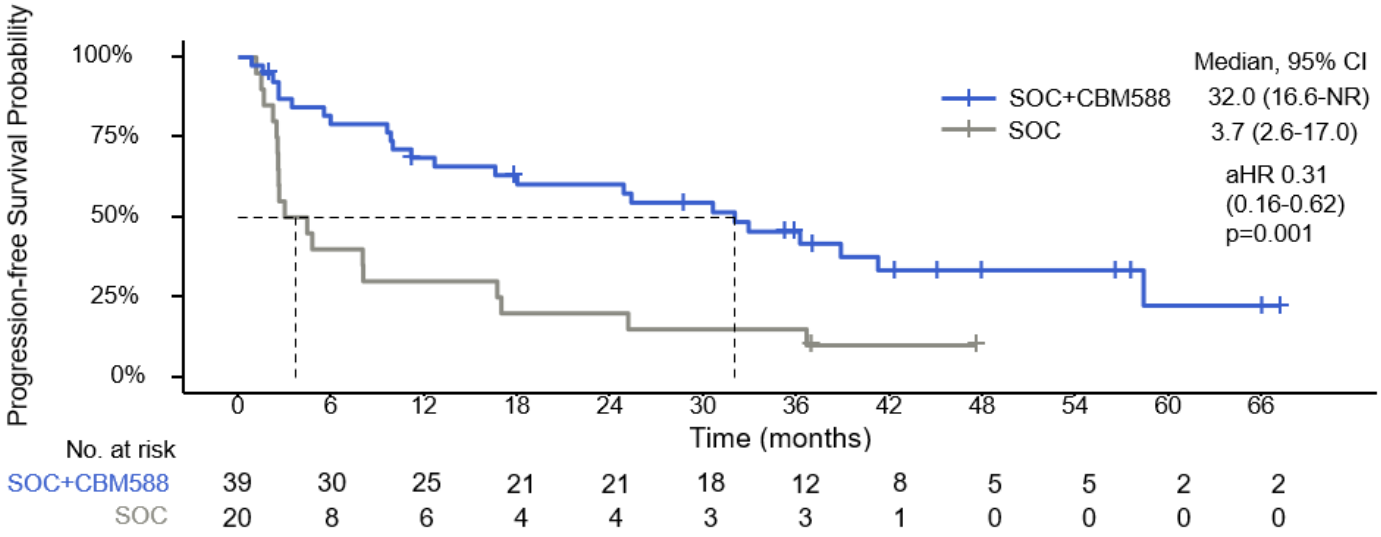
•**Akkermansia:** It factors in the presence of *Akkermansia muciniphila*, a specific gut bacterium heavily linked to positive immune responses.

Response Outcomes

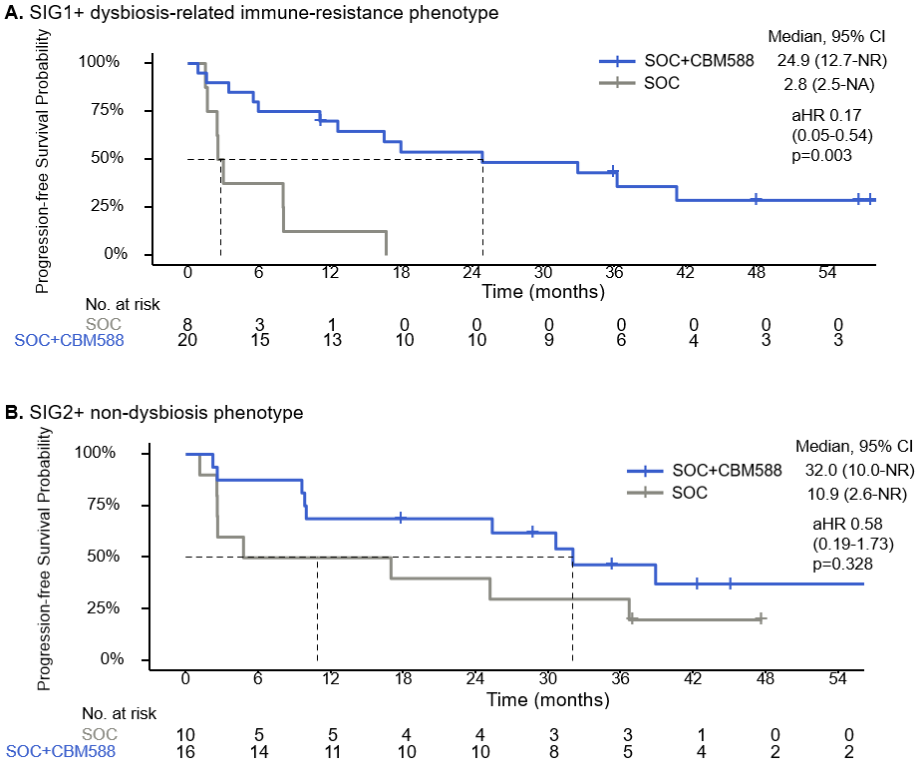
	SOC+CBM588 (N=39)	SOC (N=20)	P value
Objective response rate – no. (%)	27 (69.2%)	4 (20.0%)	0.001
Partial response	27 (69.2%)	4 (20.0%)	
Stable disease	5 (12.8%)	7 (35.0%)	
Progressive disease	6 (15.4%)	9 (45.0%)	
Disease control rate – no. (%)	31 (79.5%)	9 (45.0%)	0.0095

SOC, Standard of care (nivolumab/ipilimumab or nivolumab/cabozantinib); Disease control rate: complete response, partial response or stable disease > 6 months

Progression-free survival for overall cohort

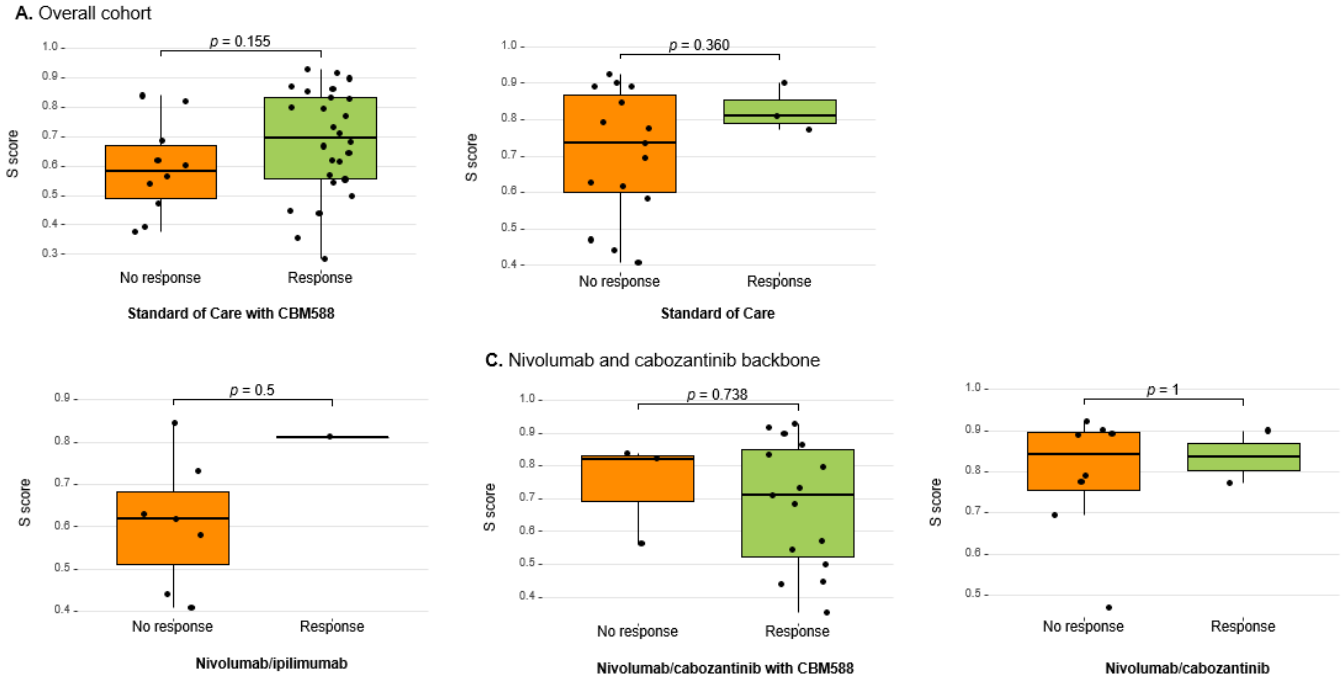


PFS by SIG1+ dysbiosis and SIG2+ non-dysbiosis

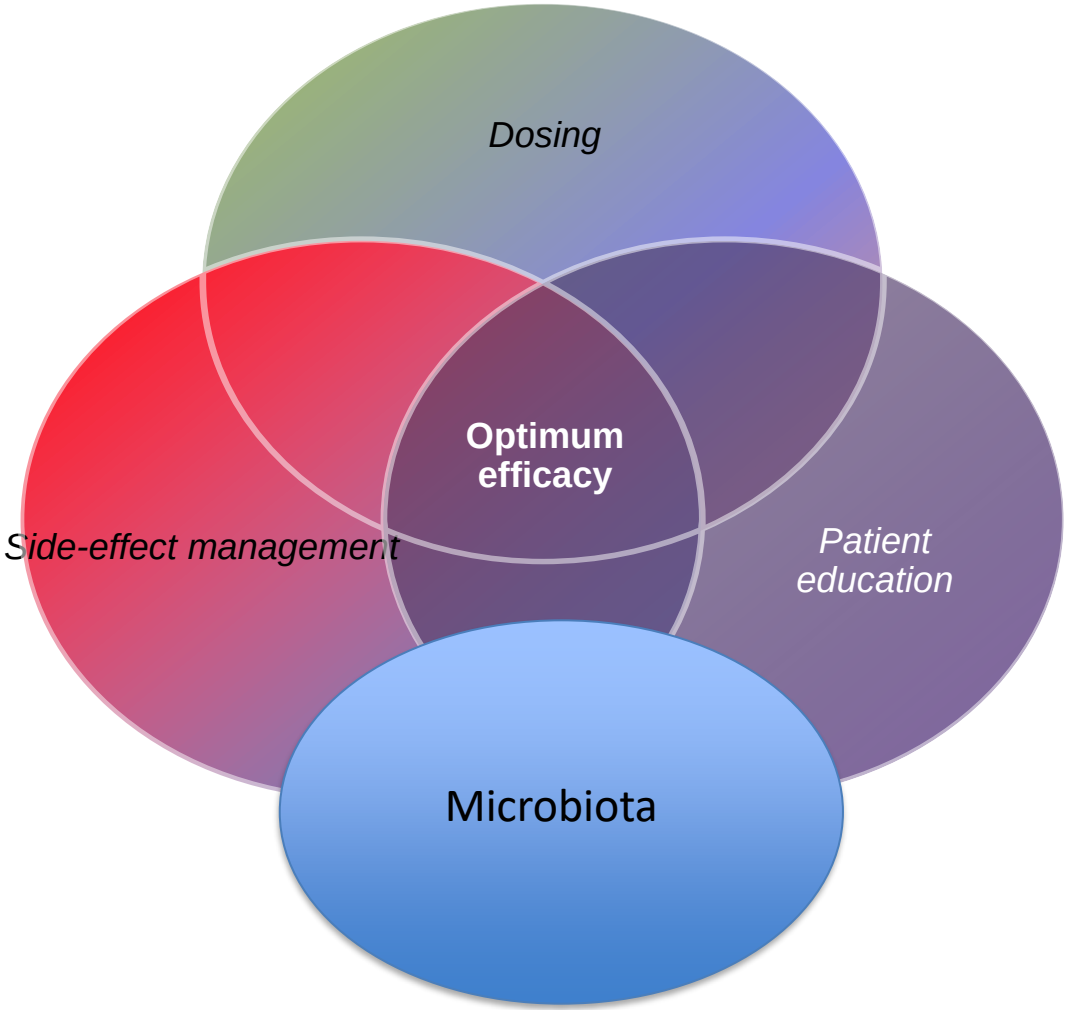


Rahul Winayak, MD

Baseline S score and response



Key factors for long term response



Gracias!!