ASCO Genitourinary Cancers Symposium

Final overall survival data and ctDNA data for savolitinib and durvalumab in advanced papillary renal cancer: CALYPSO.

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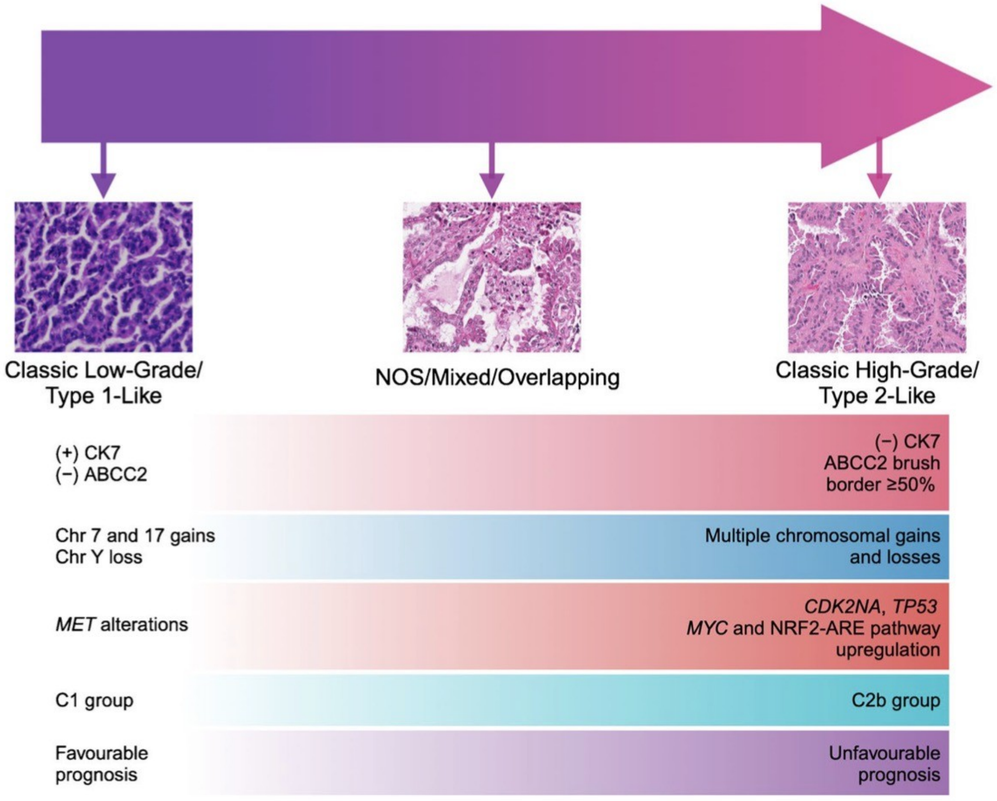
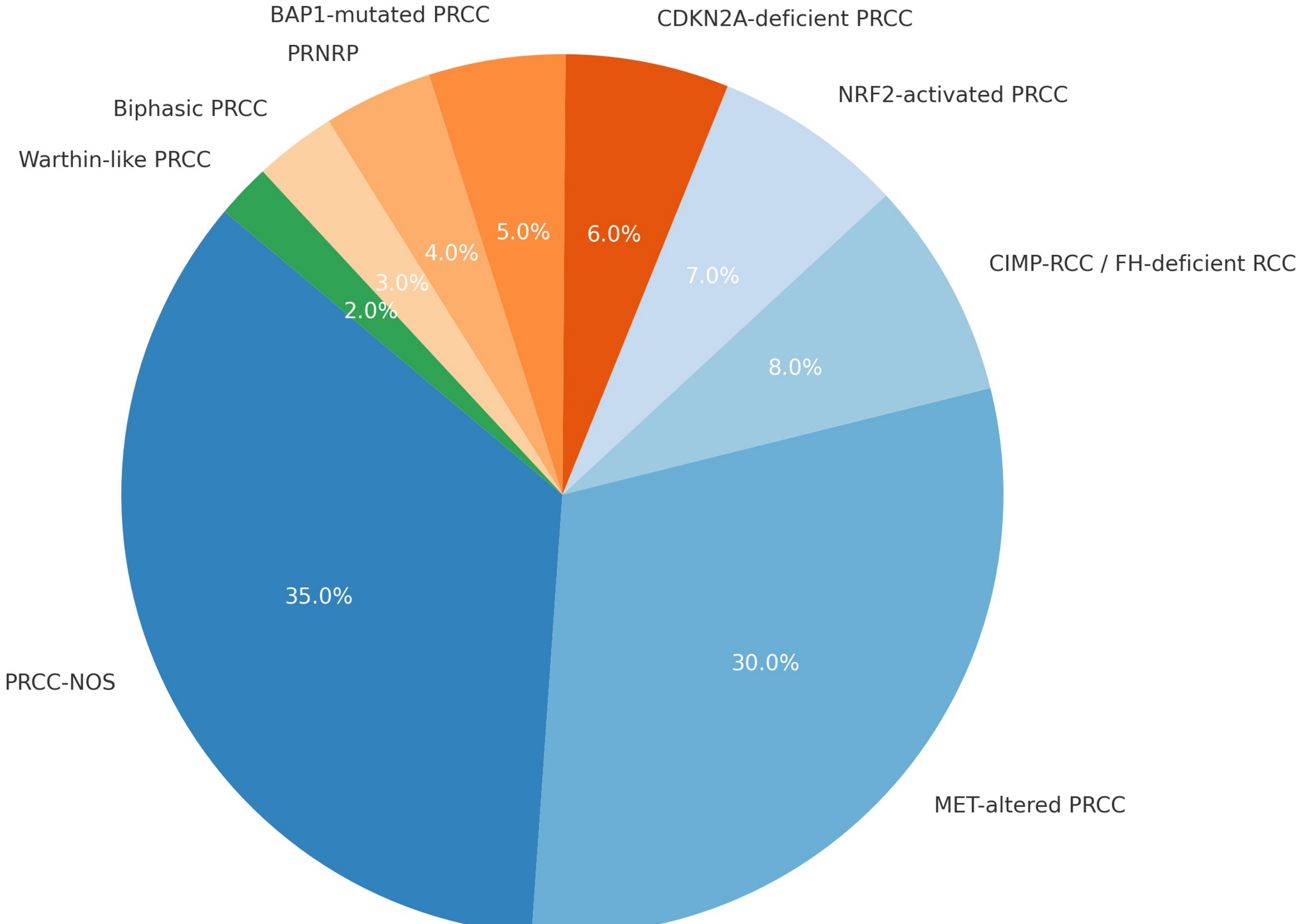
PRESENTED BY: Dr Francesca Jackson-Spence

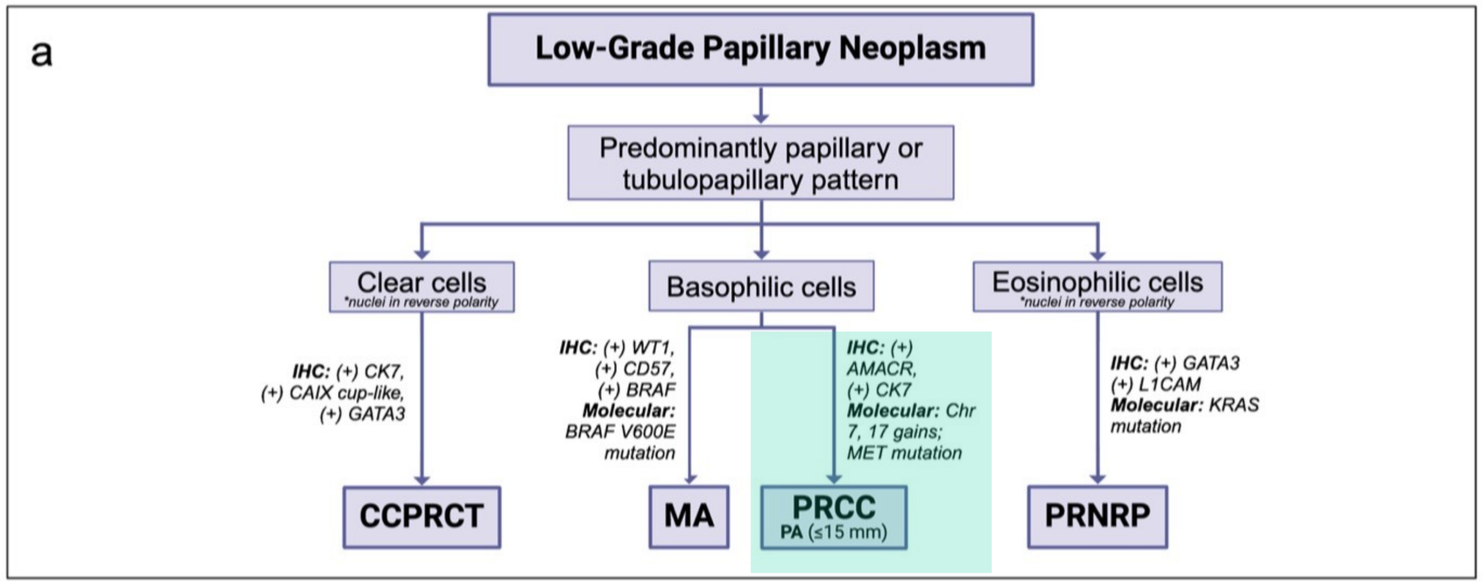
Papillary renal cancer

- Advanced papillary renal cancer (PRC) is a disease with a poor prognosis and relatively few treatment options
- WHO (2022) formally abandoned subtyping.
- DNA alterations to mesenchymal epithelial transition receptors (METs) occur in approximately 30% of patients with PRC
- The immune checkpoint inhibitor , multitargeted VEGF TKI & Preclinical data suggest a potentially positive interaction between MET and PD-L1 inhibition



MET signalling: principles and functions in development, organ regeneration and cancer, Livio Trusolino et al.


BAP1-mutated PRCC
CDKN2A-deficient PRCC
PRNRP
NRF2-activated PRCC
Biphasic PRCC
CIMP-RCC / FH-deficient RCC
Warthin-like PRCC
5.0%
6.0%
4.0%
7.0%
3.0%
8.0%
2.0%
35.0%
30.0%
PRCC-NOS
MET-altered PRCC



CCPRCT: clear cell papillary renal cell tumor, MA: metanephric adenoma, PRNRP papillary renal neoplasm of reverse polarity

WHO 2022 classification:

PRCC is defined as a malignant neoplasm **exhibiting papillary or tubulopapillary growth patterns** without specific features of other RCCs with papillary morphology

PRCC tumors are typically reactive for PAX8, AE1/AE3, Cam5.2, CD10, vimentin, AMACR, and CK7, while they are negative for CD117 (KIT).

AMACR and CK7 are the most valuable IHC markers to differentiate PRCC from other renal tumor types.

MET signalling: principles and functions in development, organ regeneration and cancer, Livio Trusolino et al.

MET Receptor Activation Cascade

1. Ligand Binding

Hepatocyte Growth Factor (HGF), Receptor dimerization.

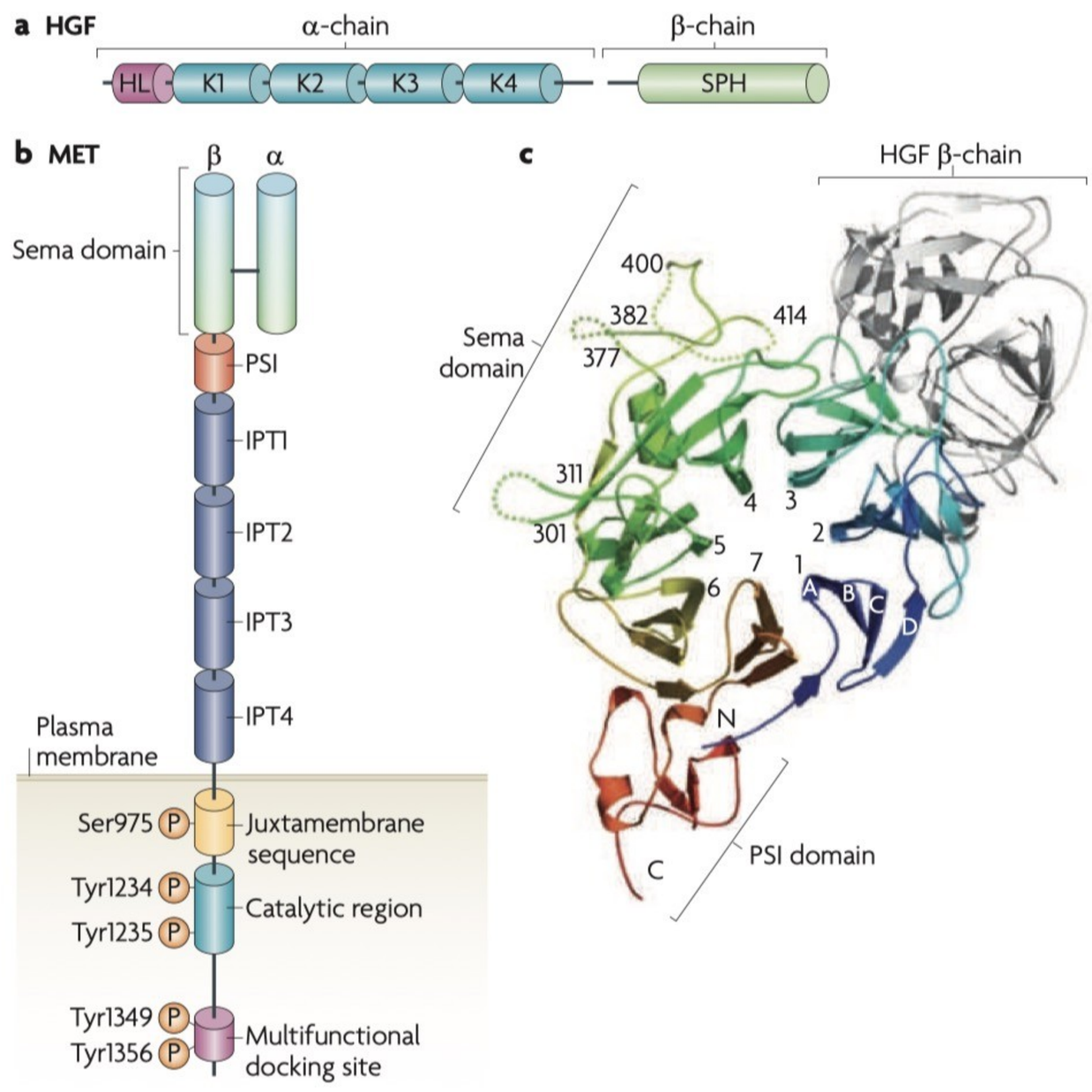
2. Kinase Activation via Autophosphorylation

Cross-phosphorylation (trans-phosphorylation) of two key **tyrosine residues** in the **activation loop** of the kinase domain: **Tyr1234**, **Tyr1235 (**turns **on the kinase activity** of MET).

3. Docking Site Formation for Signal Transduction

Two **additional tyrosine residues** in the **C-terminal tail** get phosphorylated: **Tyr1349**, **Tyr1356**: Activates Grb2, Gab1, PI3K, PLCγ, SHC, STAT3.

RAS-MAPK, **PI3K-AKT**, **STAT**, and **SRC** signaling cascades.



Cell proliferation, migration, invasion, and survival.

MET inhibitors

Feature	Savolitinib	Cabozantinib
Class	Type I highly selective MET inhibitor	Type II multi-kinase inhibitor
Binding Site	ATP-binding pocket (active conformation)	ATP pocket + adjacent hydrophobic pocket (inactive conformation)
Specificity	Highly MET-selective	Inhibits MET, VEGFR2, AXL, RET, KIT
Downstream Inhibition	Inhibits MET autophosphorylation → blocks PI3K, MAPK, STAT pathways	Same for MET, but also blocks angiogenesis via VEGFR
Clinical Implication	Ideal in biomarker-selected (MET-mutated/amplified) tumors	Broad use, including unselected pRCC and VEGF-reliant tumors
Trial Use	SAVOIR, CALYPSO, SAMETA	PAPMET, CheckMate 9ER

CALYPSO: Phase II study investigating savolitinib in combination with durvalumab in advanced papillary renal cancer.

Papillary (PRC) cohort:

n=41

Patients with:
- Advanced papillary RCC
- Measurable disease as per RECIST v1.1
- VEGF naïve/treatment refractory
- ECOG 0-1

Savolitinib 600mg OD starting D1

+

Durvalumab 1500mg 4 weekly added D29

Treatment until progression or loss of clinical benefit. Follow up 2 years

OS follow up

Primary endpoint
- cRR

Key secondary endpoints:
- PFS
- OS
- DoR
- Best response at 24weeks
- Safety

cRR in ITT: 32%

cRR in MET-driven: 53%

Median FU: 14.1months
(CI: 7.4 - 28.4)

No new safety signals

ctDNA (baseline) | **ctDNA (week 4)** | **ctDNA (week 4-16)** | **ctDNA (PD)**

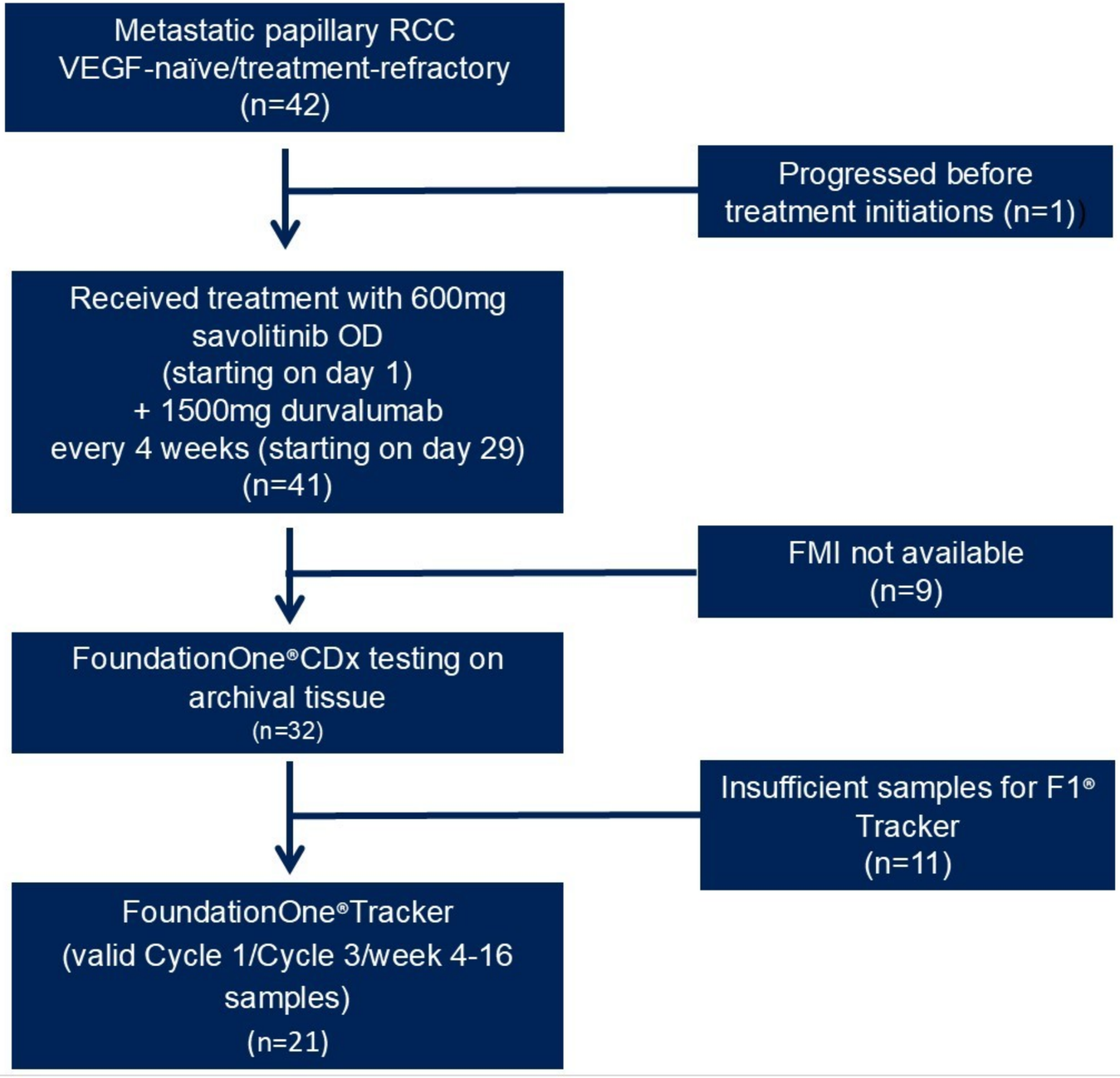
Suarez et al, JCO,2023

Endpoint	Overall Cohort	MET-driven subgroup
Confirmed RR	29% (did not meet primary endpoint)	**53%**
Median PFS	4.9 months	**12.0 months**
Median OS	14.1 months	**27.4 months**
1-year OS rate	54.3%	**70.6%**
Duration of Response	9.4 months	**11.5 months**

Safety Outcomes:

- Treatment-related adverse events (TRAEs): 83%
- Grade ≥3 TRAEs: 41%
- Most common toxicities: nausea, edema, fatigue, vomiting
- Serious AEs (SAEs): 39%
- One grade 5 TRAE (cerebral infarction)

ctDNA analysis methods



Methods of Biomarker analysis in CALYPSO

- **ctDNA analysis**
  - FoundationOne®CDx analysis (CGP) was performed on tissue samples of PRC patients enrolled on the CALYPSO trial (n=32)
  - FoundationOne®Tracker used for ctDNA analysis (n=21) 48% positive
- **MET-driven status**
  - Defined as: chromosome 7 gain, MET amplification, MET kinase domain variations, or hepatocyte growth factor (HGF) amplification 41% MET-driven
- **PD-L1 analysis**
  - Centrally assessed using the VENTANA PD-L1 (SP263) assay
  - Tumour +/or immune staining of ≥1% defined positivity 66% positive
- TMB analysis
  - TMB assessed via FoundationOne®CDx
  - TMB above median (>) compared to TMB median or below (≦)
    Median TMB is 2.52mut/Mb.

Baseline profiling — FoundationOne CDx

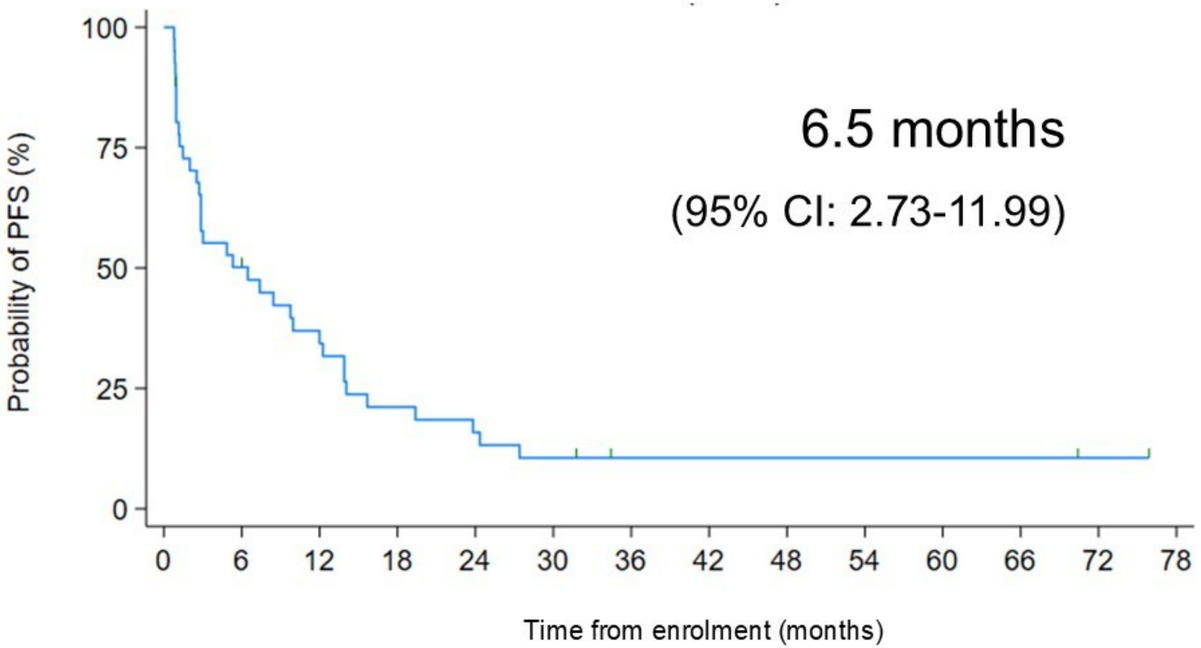
- FDA-approved, tissue-based NGS assay interrogating the full coding region of **324 cancer genes** plus genomic signatures (TMB, MSI)
- Detects all clinically actionable **MET** events
- Variant reported with exact genomic coordinates and quantitative VAF (tumour's molecular fingerprint)

Personalised surveillance — FoundationOne Tracker

- Builds a **custom hybrid-capture panel** using the MET and co-alterations identified by F1CDx (≥300-gene template) to track patient-specific variants (PSVs) in plasma
- Ultra-sensitive ctDNA detection
- Longitudinal quantification of tumour burden and early identification of resistance before radiographic progression

Final PFS and OS in ITT population

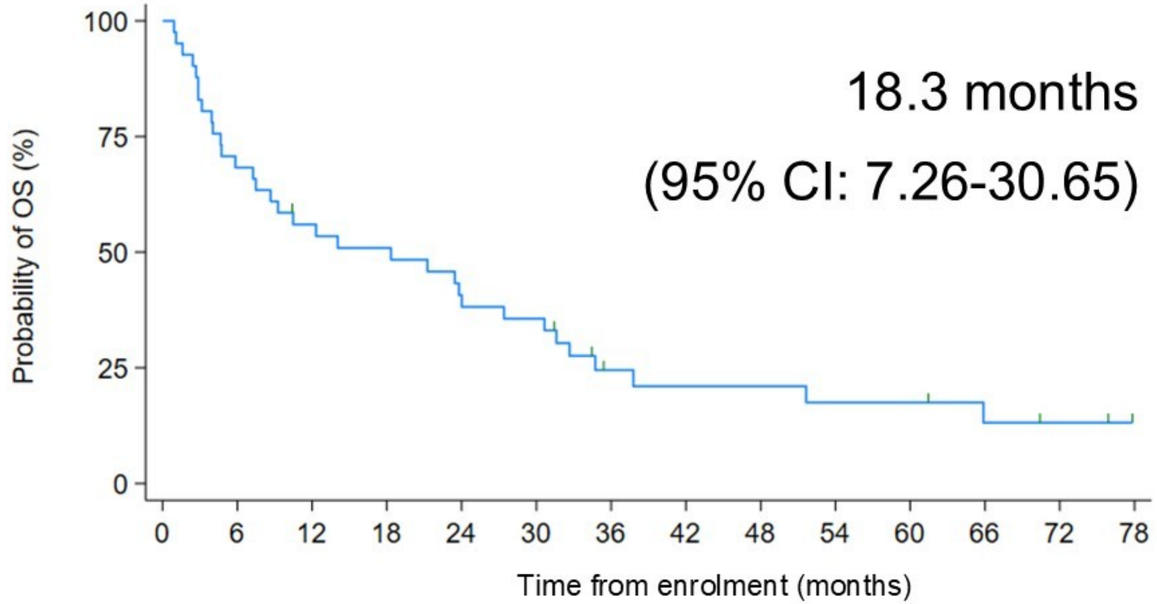
ITT population Progression-Free Survival



6.5 months

(95% CI: 2.73-11.99)

ITT population Overall Survival



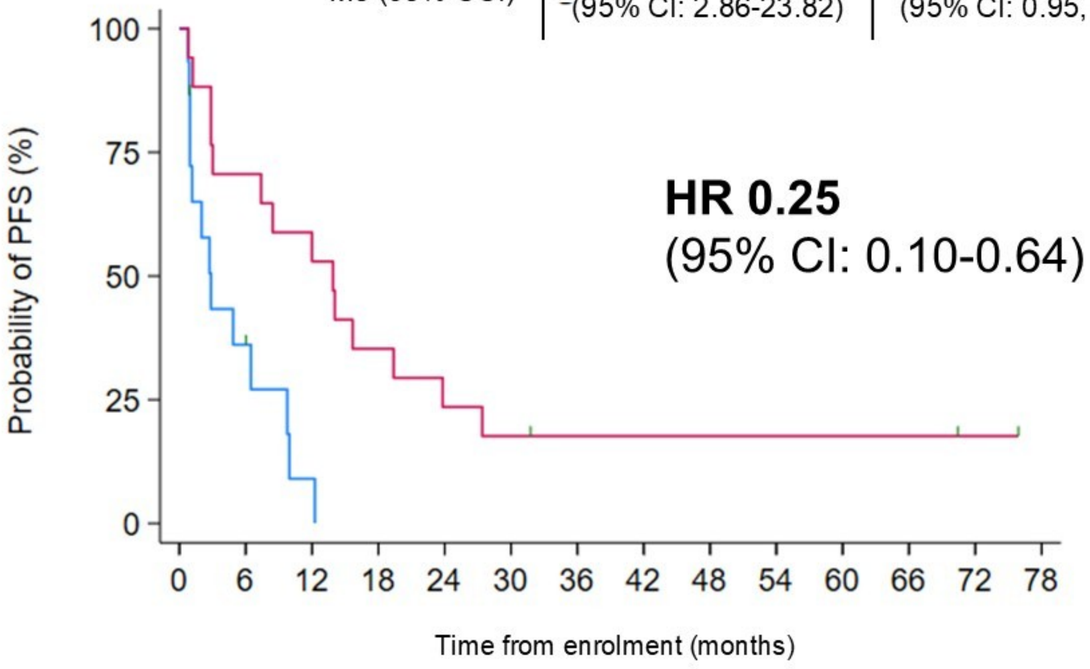
18.3 months

(95% CI: 7.26-30.65)

Final PFS and OS in MET-driven population

MET-driven Progression-Free Survival

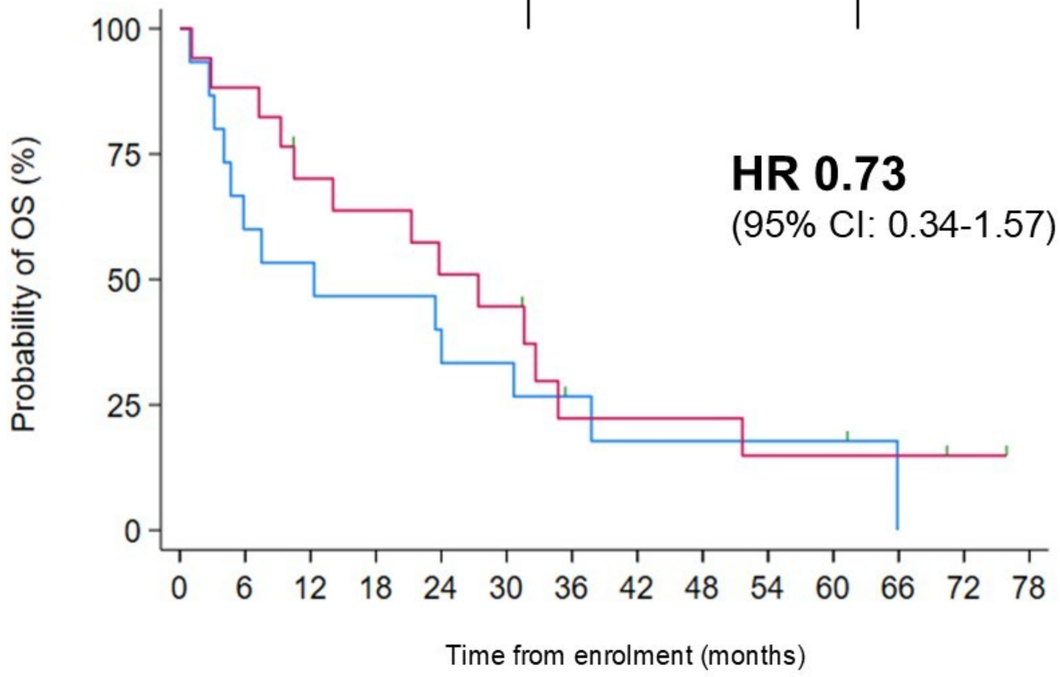
	MET-driven (n=17)	Non-MET-driven (n=15)
Median PFS Mo (95% CCI)	**13.9** -(95% CI: 2.86-23.82)	2.9 (95% CI: 0.95, 9.7)



HR 0.25
(95% CI: 0.10-0.64)

MET-driven Overall Survival

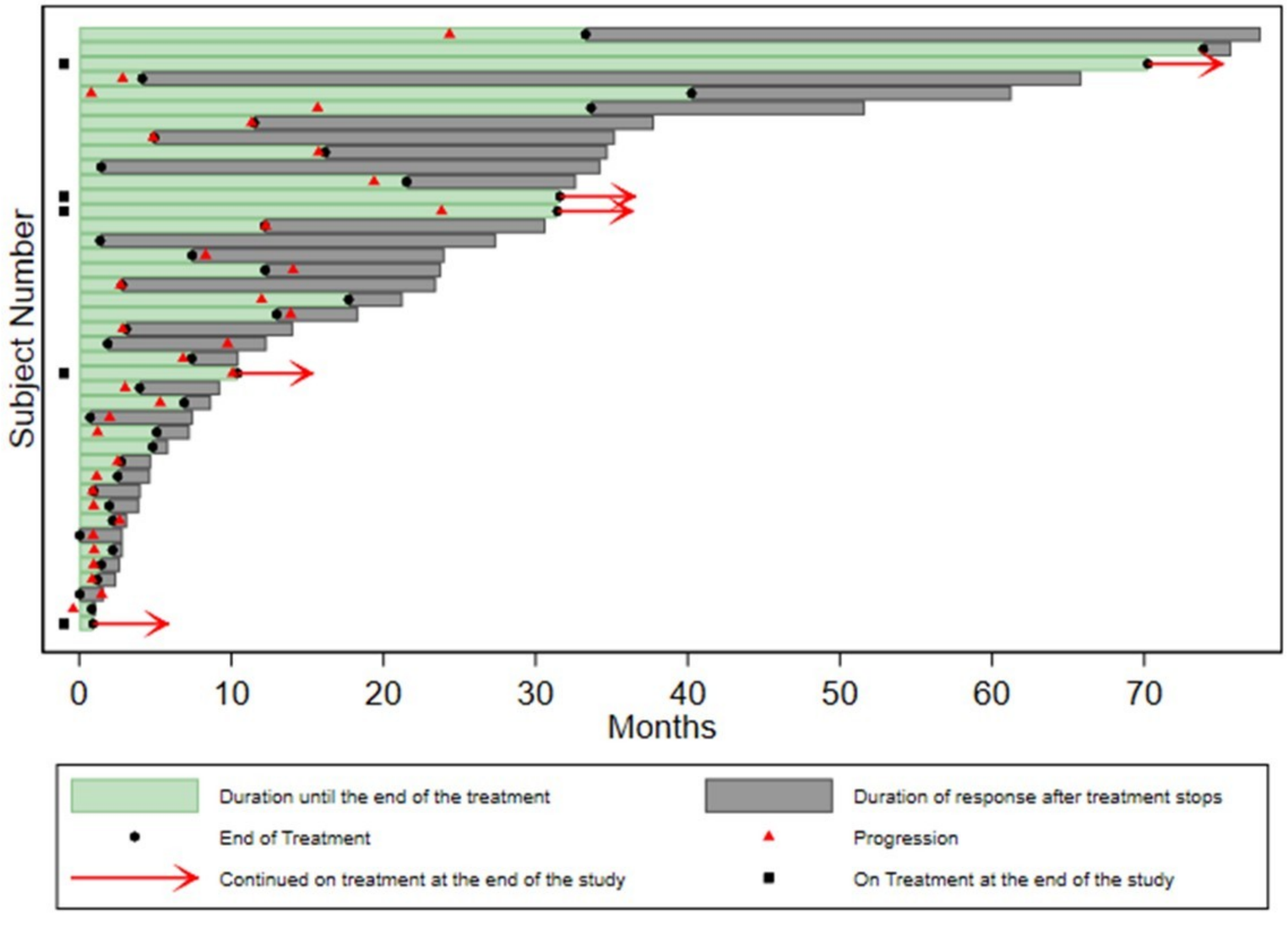
	MET-driven (n=17)	Non-MET-driven (n=15)
Median OS Mo (95% CCI)	**27.4** (95% CI: 9.27-34.73)	12.3 (95% CI:3.15-30.65)



HR 0.73
(95% CI: 0.34-1.57)

nths)

ITT population: duration of response



Median duration of response:

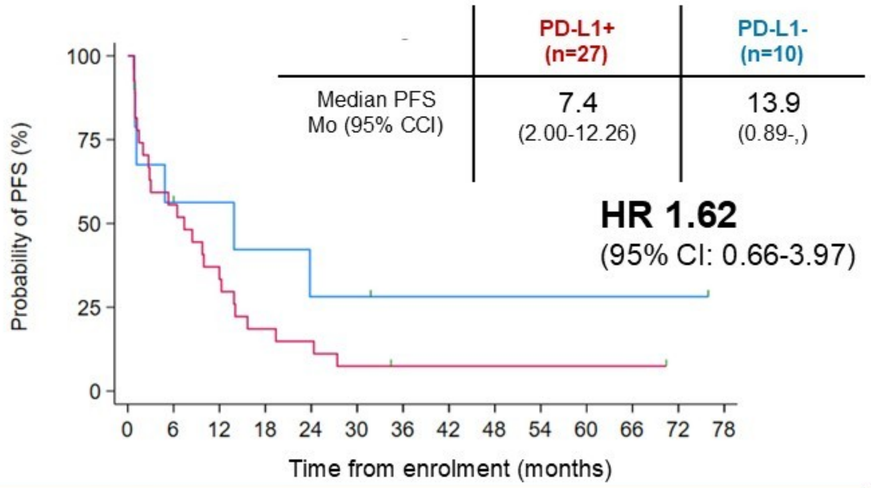
11.3 months

(95% CI: 5.52- NR)

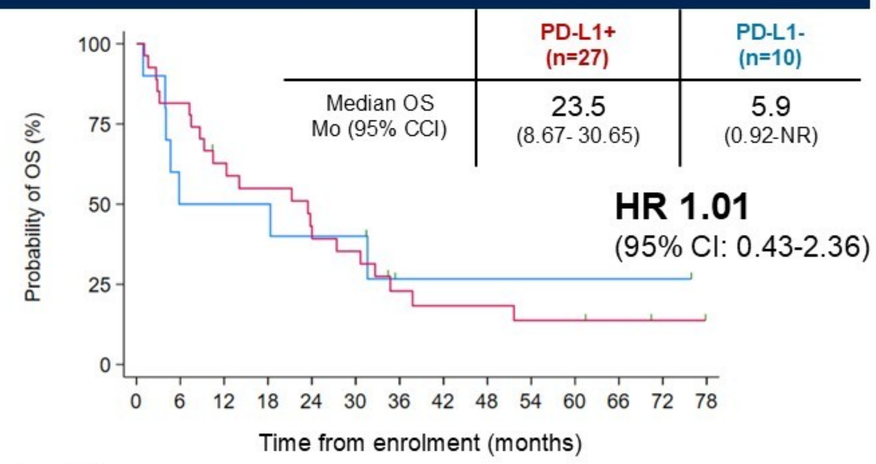
Exploratory analysis according to PD-L1 and TMB status

PD-L1

PD-L1 Progression-Free Survival

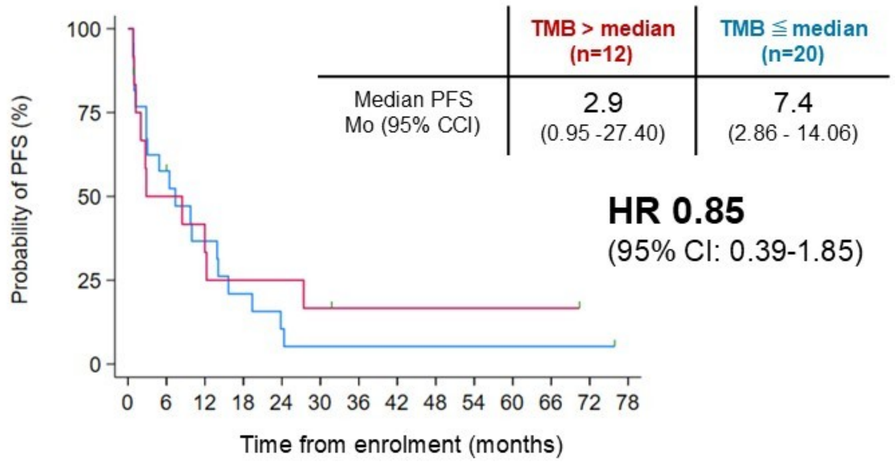


PD-L1 Overall Survival

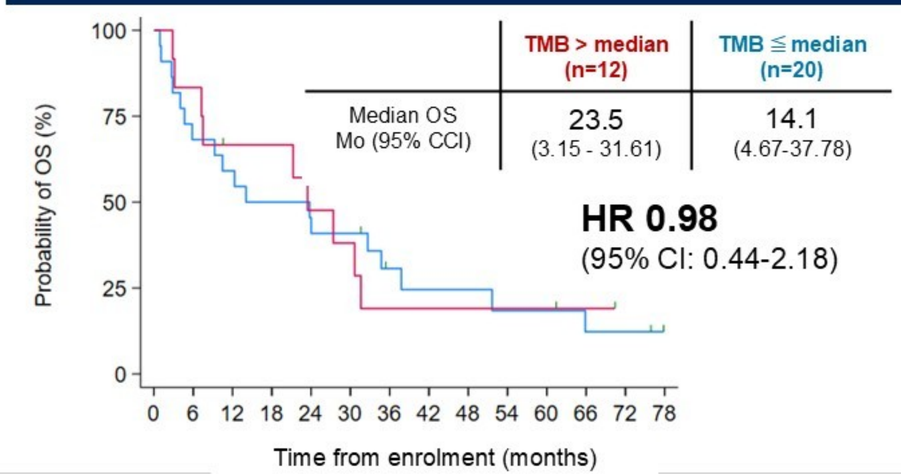


TMB

TMB Progression-Free Survival



TMB Overall Survival

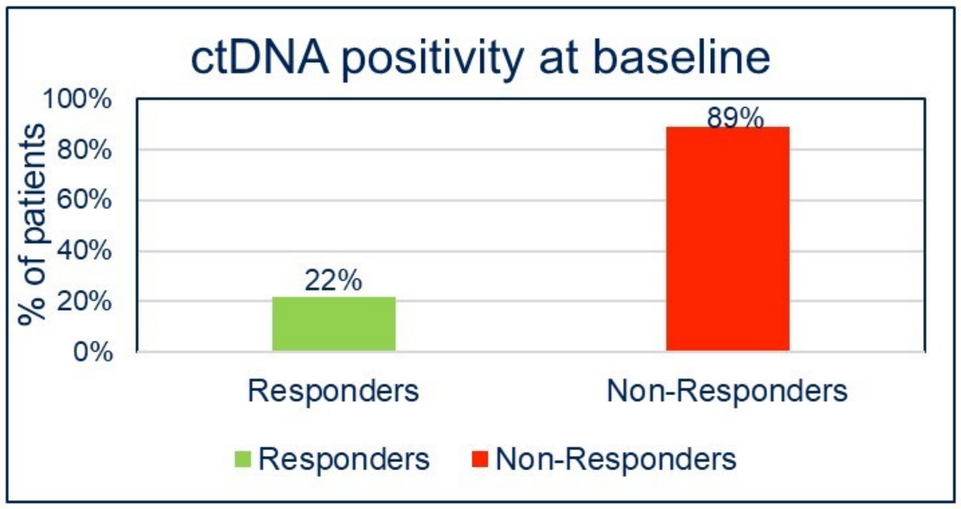


Median TMB 2.52mut/Mb

Results: ctDNA status according to best response

10/21 (48%) of patients ctDNA positive at baseline

Only 1 patient had trackable MET alterations



Subject ID	Baseline	Week 4-16	PD	Best response	Prior VEGF TKI	MET-driven	PD-L1 Positive
S032	●	○		PR			
S081	●	○		PR			
S044	○	○		PR			
S033	○	○	○	PR			
S066	○	○		PR			
S107	○	○	○	PR			
S091	○			PR			
S004		○		PR			
S030	●			SD			
S075	●			SD			
S090	●	●		SD			
S053	○	●		SD			
S013	○	○		SD			
S057	○	●		SD			
S060	○			SD			
S010	●			PD			
S098	●	●		PD			
S067	●	●		PD			
S094	●	●	●	PD			
S097		●	●	PD			
S086	●			PD			

Green = responders (CR or PR)

Red = Non-responders (SD or PD)

● ● = ctDNA positive

○ = ctDNA negative

= MET-driven

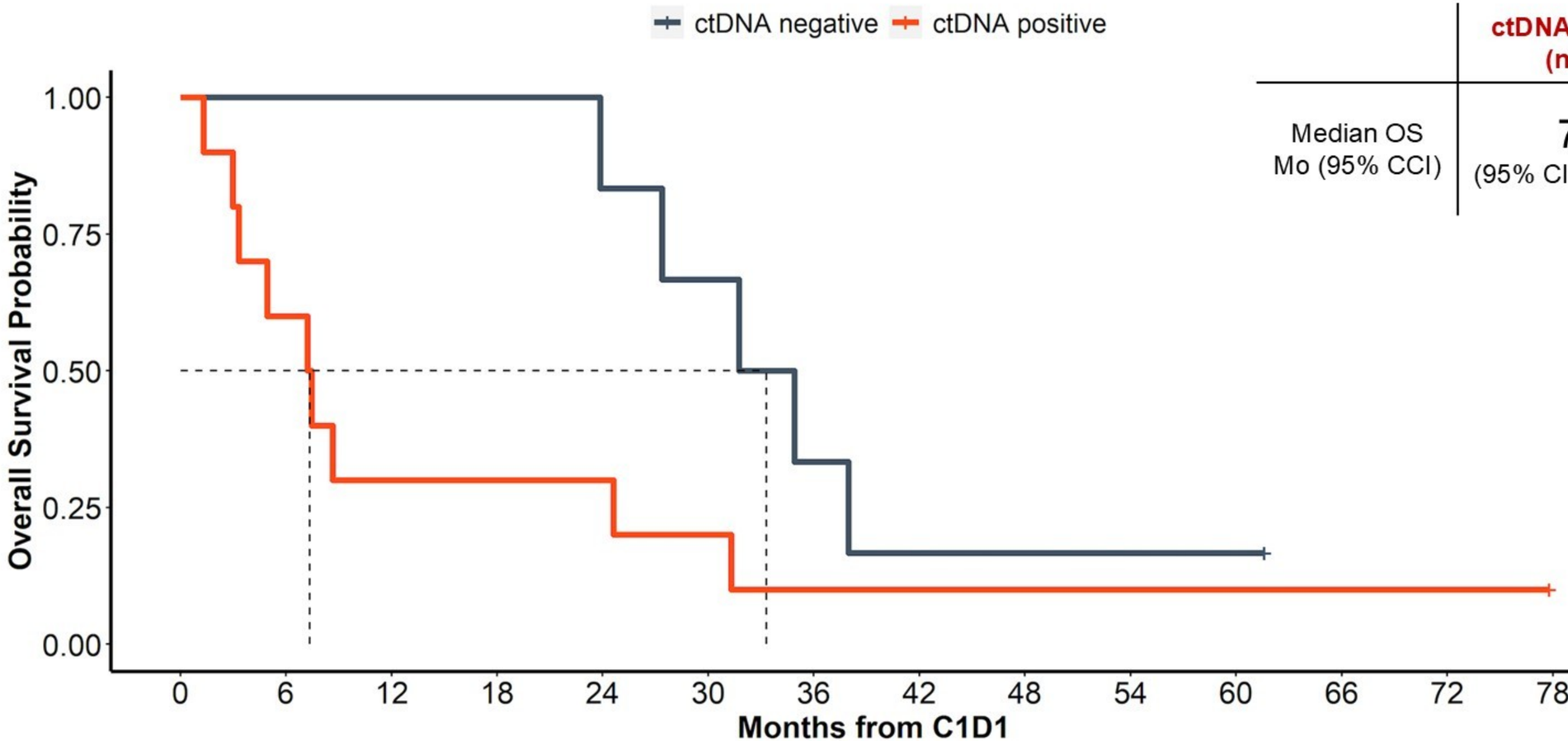
= PD-L1 positive

= prior VEGF

PRESENTED BY: Dr Francesca Jackson-Spence

Results: ctDNA status at baseline

Overall survival: ctDNA status at baseline

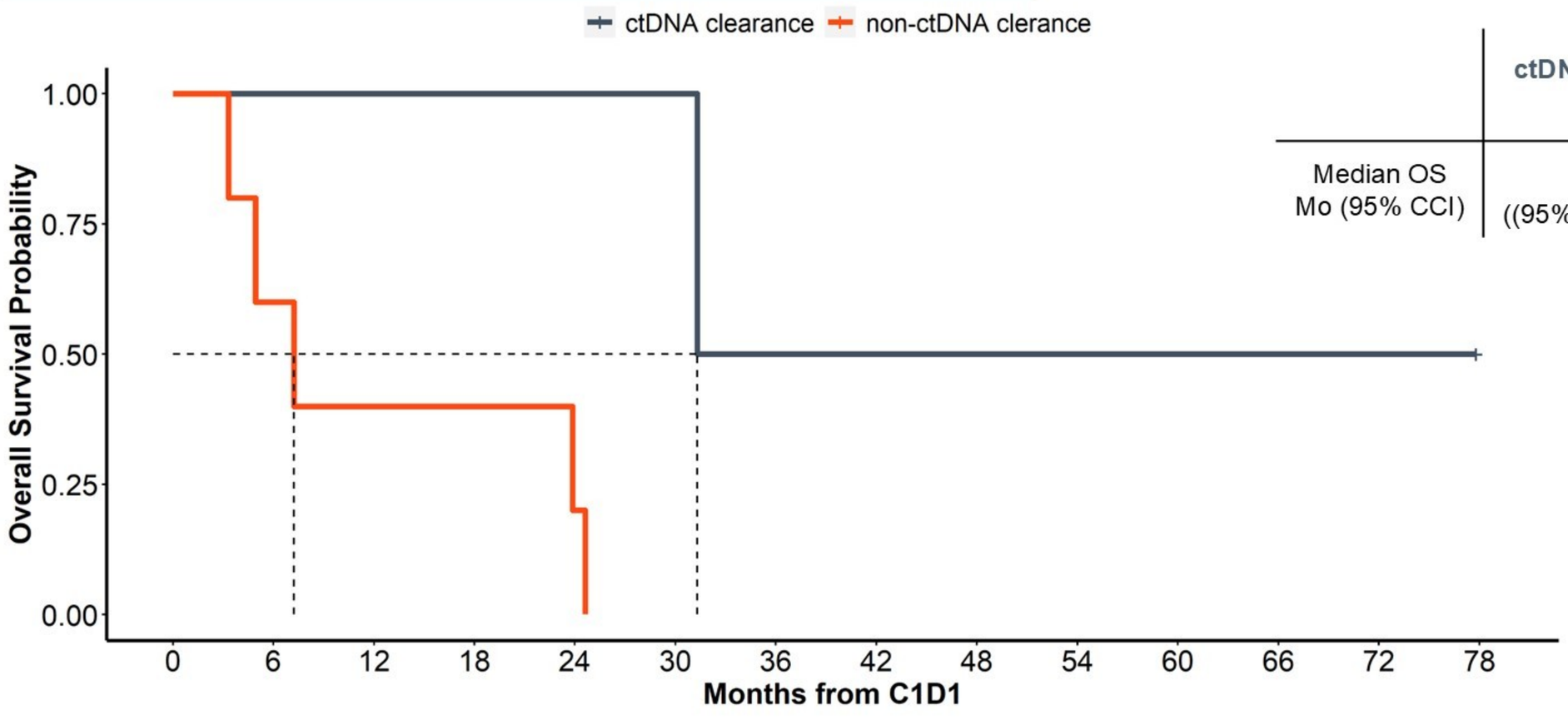


	ctDNA positive (n=10)	ctDNA negative (n=6)
Median OS Mo (95% CCI)	7.3 (95% CI: 3.3 – NA)	33.3 (95% CI:27.4 - NA)

HR 2.73
(95% CI: 0.88- 8.47)

Results: ctDNA status clearance

Overall survival: ctDNA clearance on treatment

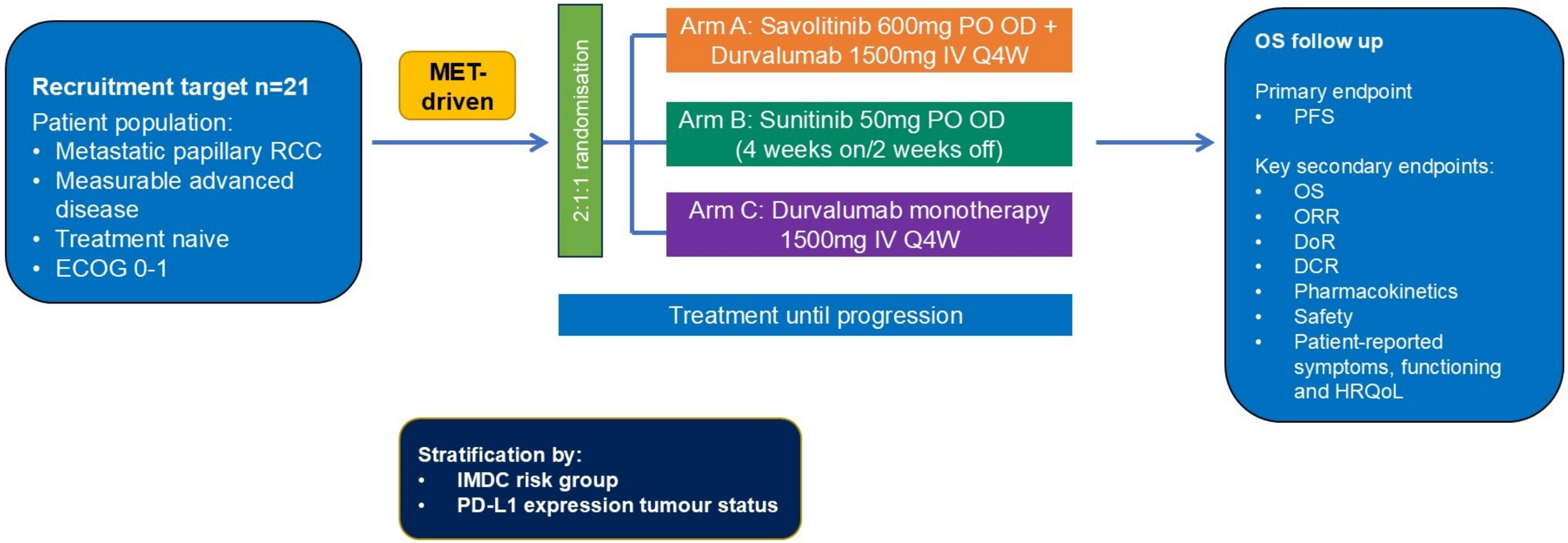


	ctDNA clearance (n=2)	No ctDNA clearance (n=5)
Median OS Mo (95% CCI)	31.3 ((95% CI: 31.3 -NA)	7.2 (95% CI: 4.93 - NA)

HR >10
(95% CI: 0.00- inf)

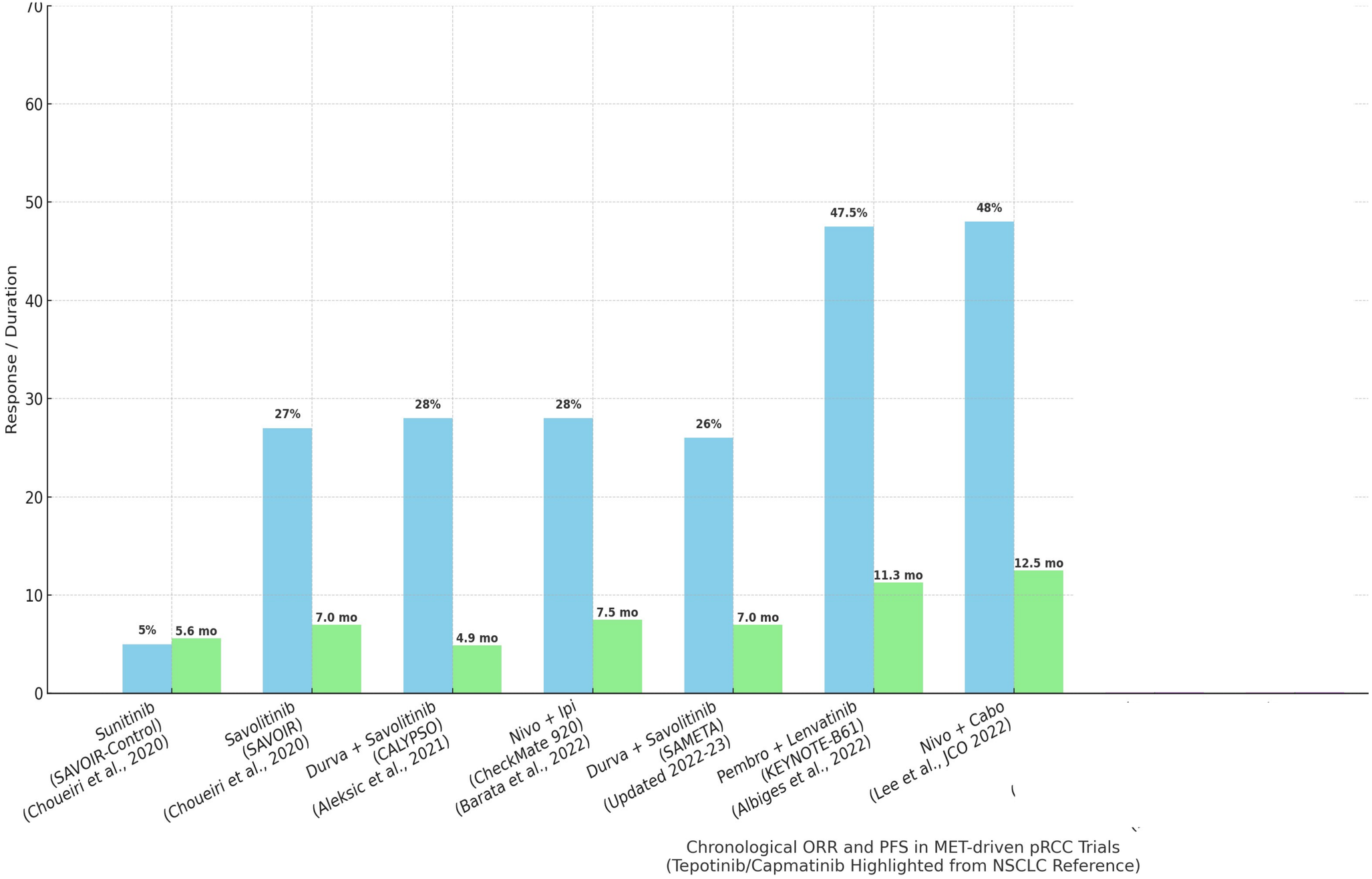
2 patients cleared ctDNA at week 4-16 on savolitinib + durvalumab.
Both achieved PR

SAMETA: An open-label, three-arm, multicenter, phase III study of savolitinib + durvalumab versus sunitinib and durvalumab monotherapy in patients with MET-driven, unresectable, locally advanced/metastatic papillary renal cell carcinoma (PRCC)

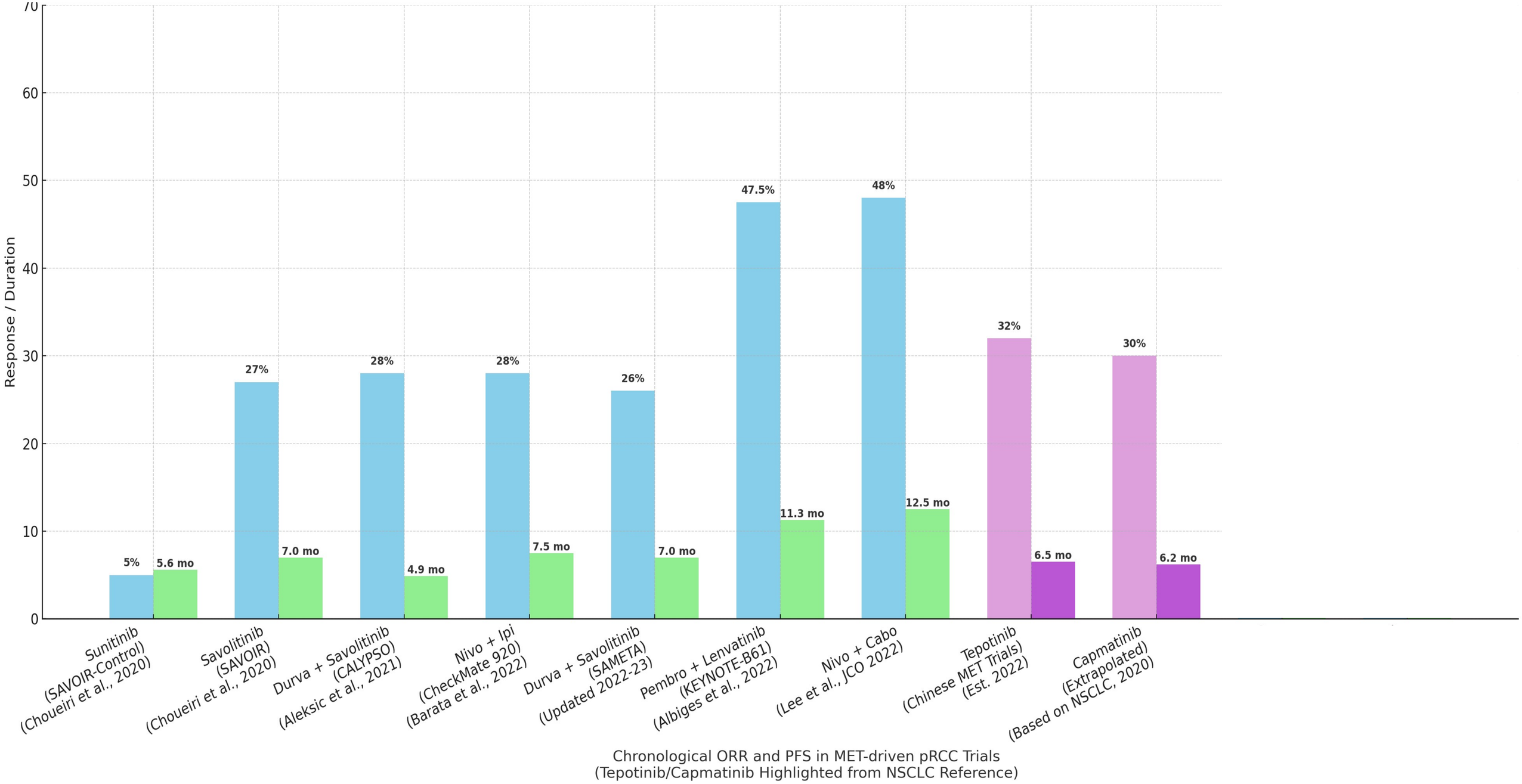


NCT05043090

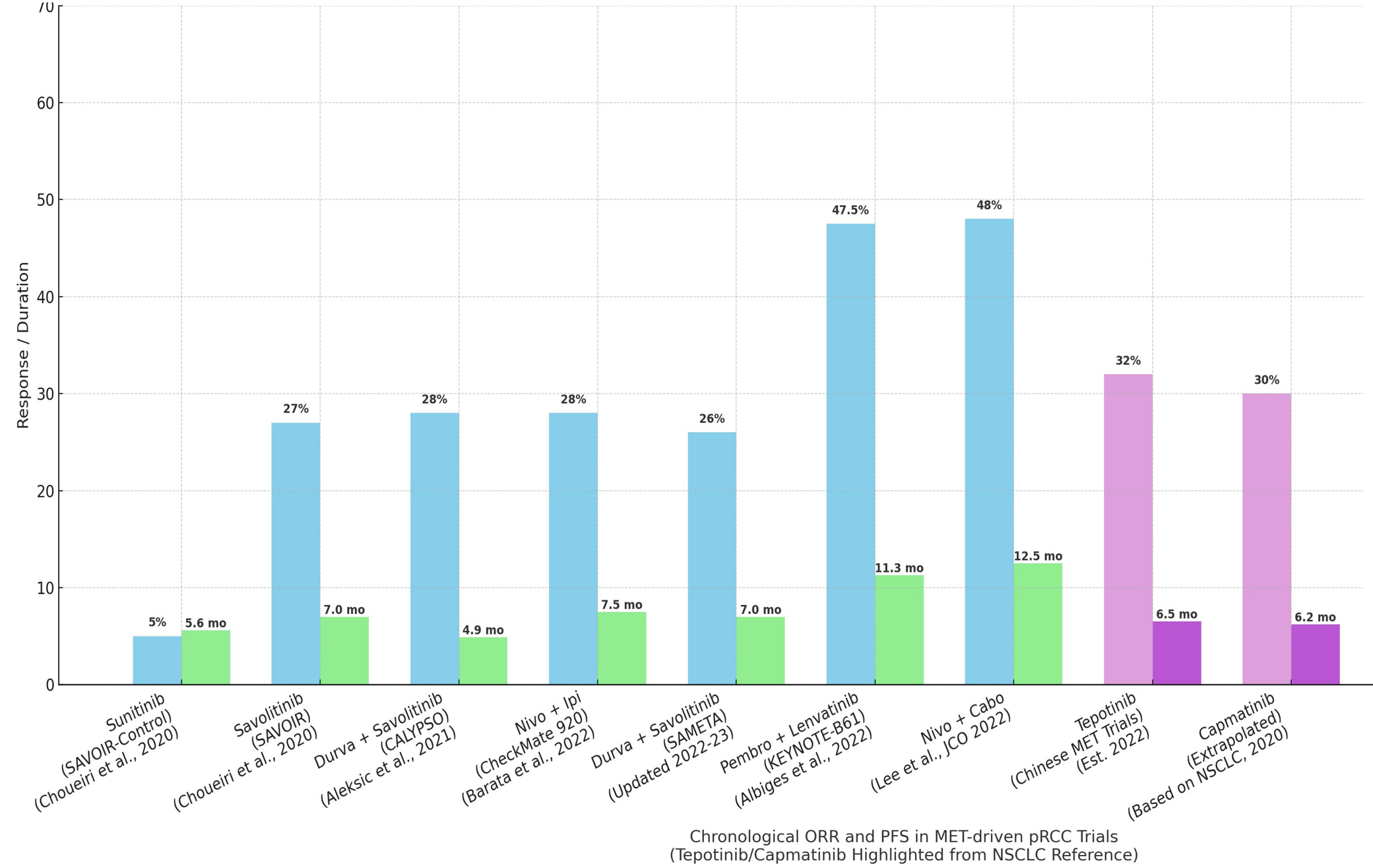
MET driven PRCC trials



MET driven PRCC trials



MET driven PRCC trials



- Papmet 2: (phase 2): cabozantinib atezolizumab
- Paxipem (French study) axitinib + pembrolizumab
- Zenzilitinib with nivolumab

Strengths

• ctDNA monitoring
• Compelling data in PRCC space
• Results independent of PD-L1, TMB, prior VEGF status

Opportunities

• Paves way for SAMETA trial
• Explore pathway crosstalk; guide post-progression therapy
• Highlights prognostic value of ctDNA clearance

Weaknesses

• Small sample size
• Short follow-up
• No standardized methodology

Threats

• MKIs + checkpoint inhibitors
• Emerging inhibitors: ABCC1, NRF2

Conclusions

- Phase II study shows savolitinib + durvalumab combination has activity in papillary renal cancer
- Tumour responses enriched in the MET-driven group with median OS 27.4 months
- Response irrespective of PD-L1 status and TMB status
- 48% were ctDNA positive at baseline
- ctDNA status at baseline has prognostic value
- Few patients had trackable MET alterations
- The promising efficacy and safety profile for savolitinib in combination with durvalumab in MET-driven PRC is further investigated in the SAMETA trial (NCT05043090).