

6-7 JULIO 2023

GU-Alliance for Research
and Development

guardsymposium2023

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GUARD SYMPOSIUM

Precision medicine - new scenarios in kidney cancer

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Spanish National Cancer Research Centre (CNIO)

Genomic definition of renal cell carcinoma (RCC)

- Molecular
- Prognostic

- Intratumor heterogeneity

- Predictive



KIRC → ccRCC

KIRCH → chRCC

KIRP → pRCC

TRACER_x

→ ccRCC

Turajlic Cell 2018 x2
Mitchell Cell 2018

Single cell

→ ccRCC

Clinical trials
genomic data

→ ccRCC

IMmotion150/151
CheckMate09/10/25
JAVELIN Renal 101

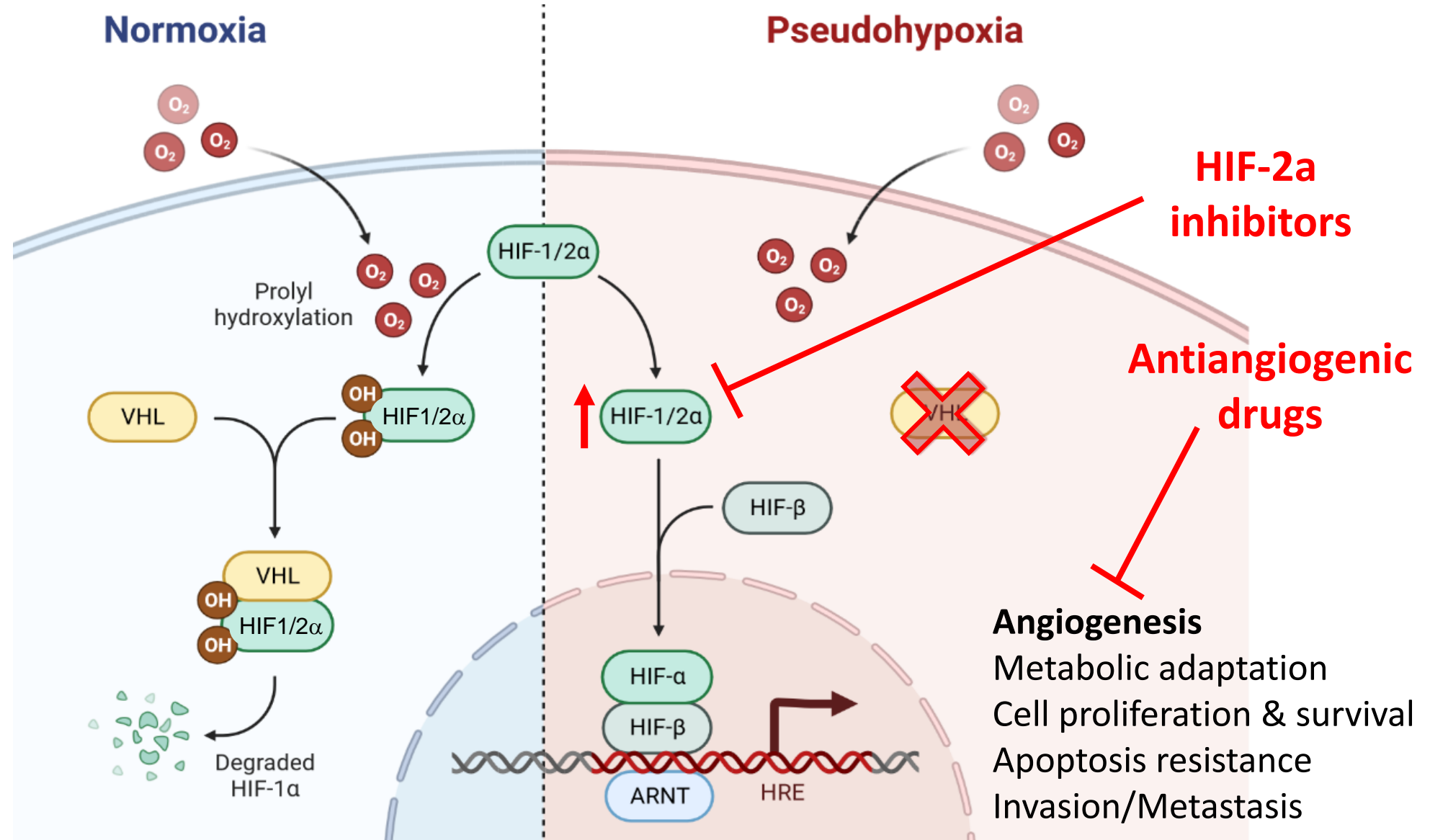
TCGA, Nature 2013
Davis Cancer Cell 2014
Linehan, N Engl J Med 2016

Li Cancer Cell 2022

McDermott Nat Med 2018
Motzer Cancer Cell 2020
Braun, Nat Med 2020
Motzer Nat Med 2020

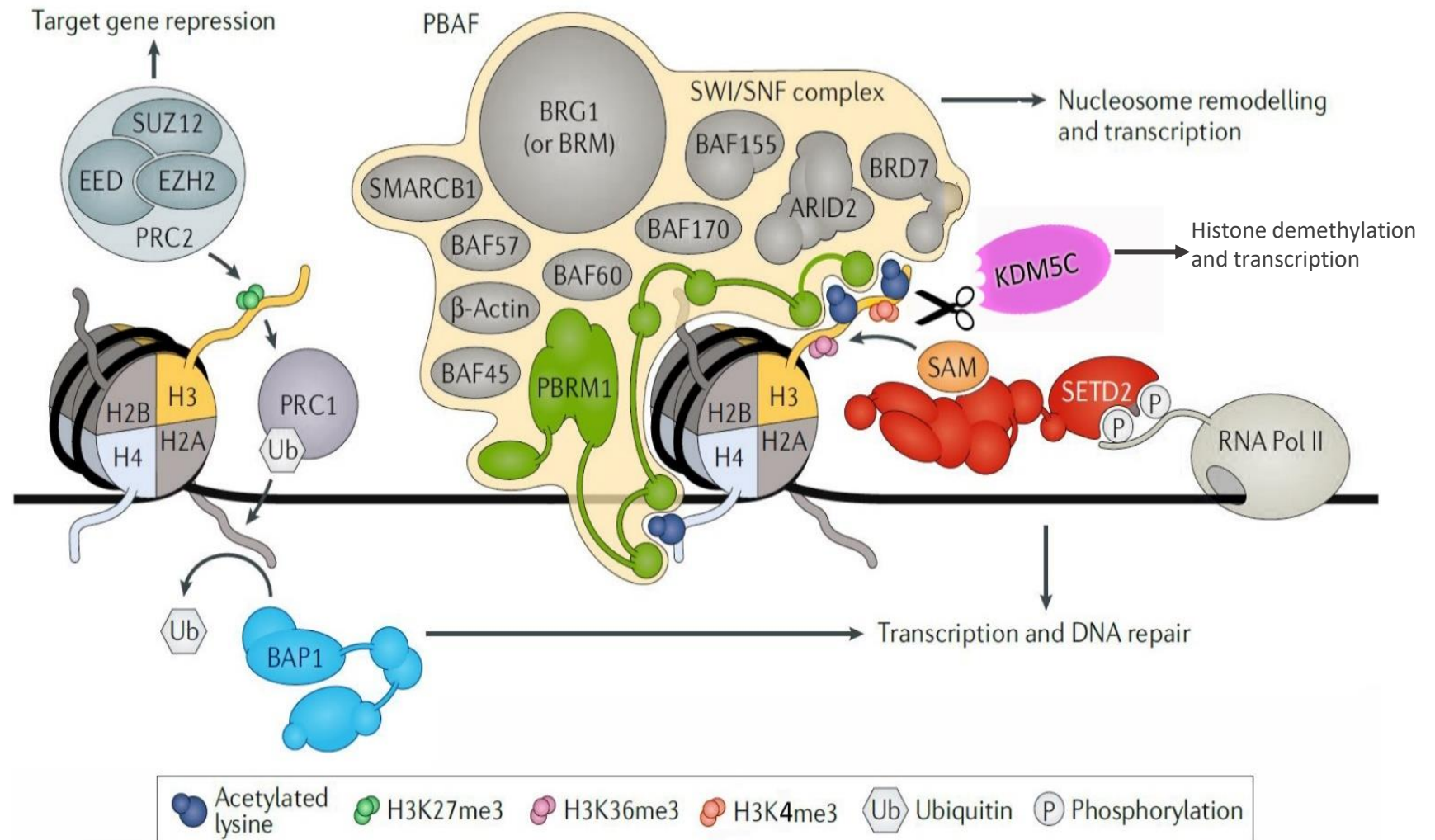
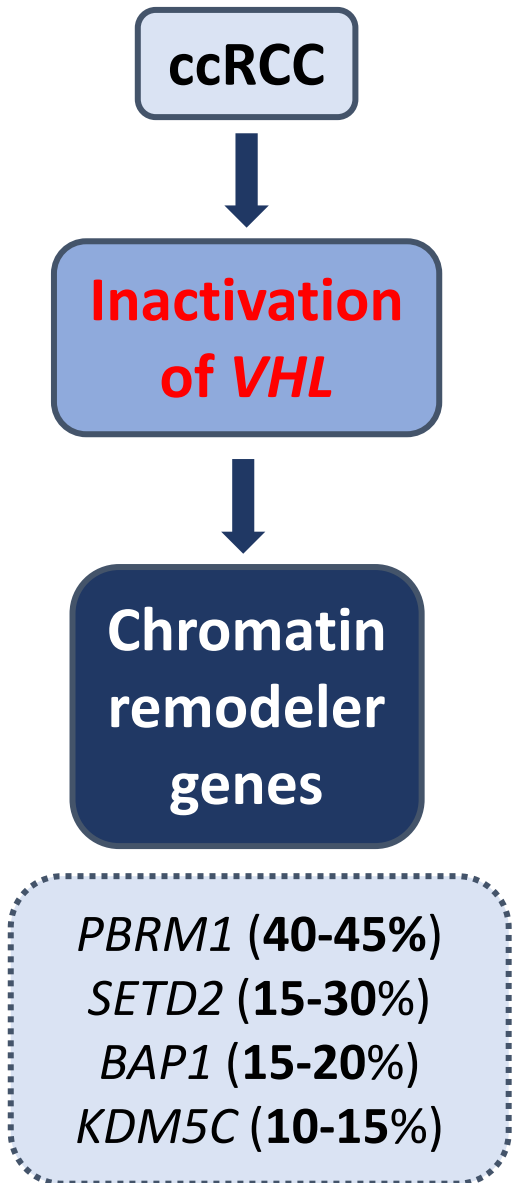
Clear cell RCC: homogeneity in driver gene (VHL)

ccRCC
↓
Inactivation of VHL



Clear cell RCC: heterogeneity in secondary alterations

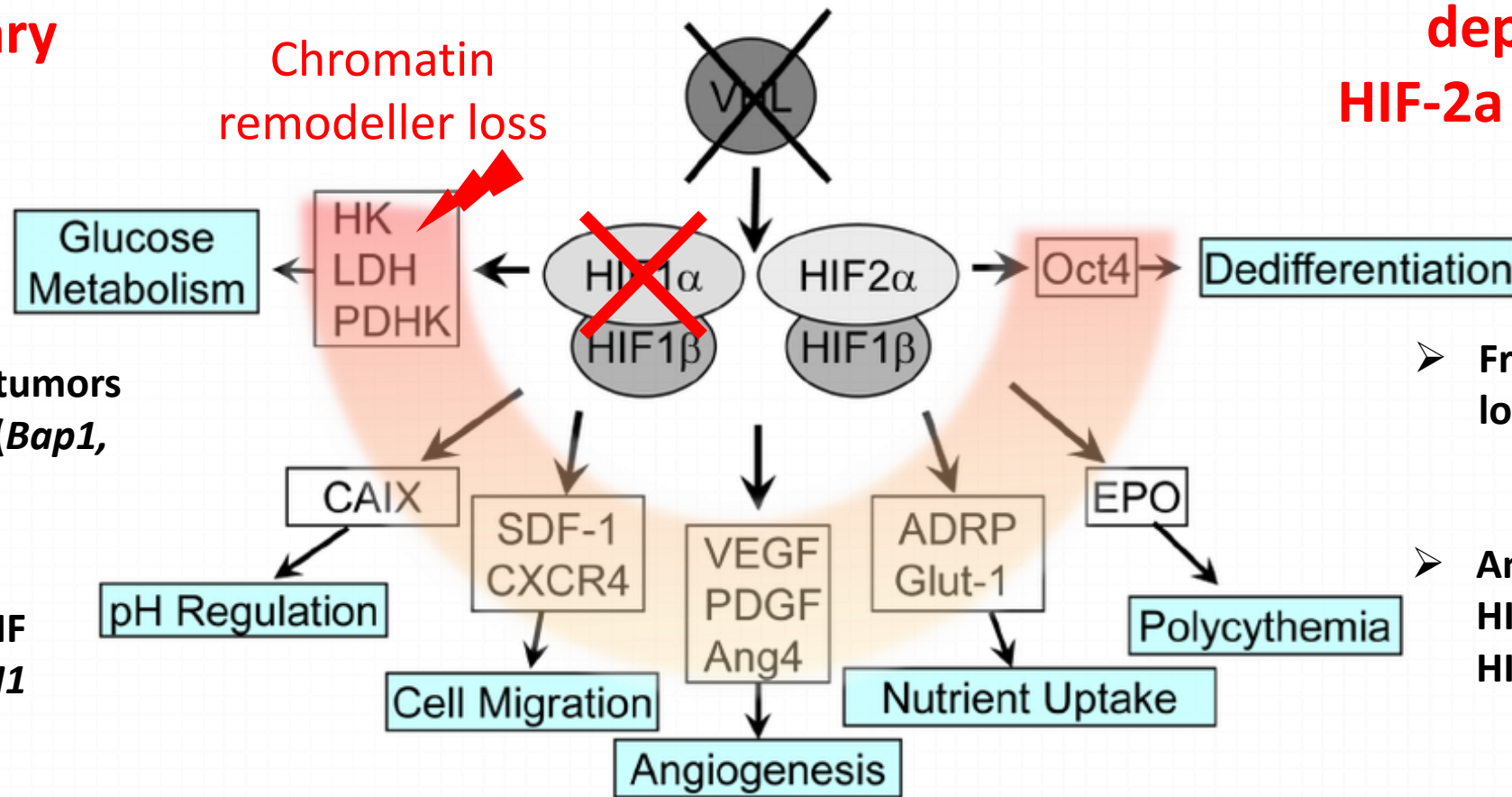
Chromatin remodelers in ccRCC



ccRCC molecularly defined by:

• **VHL inactivation plus secondary events**

• **Fundamental dependency on HIF-2α (not HIF-1α)**



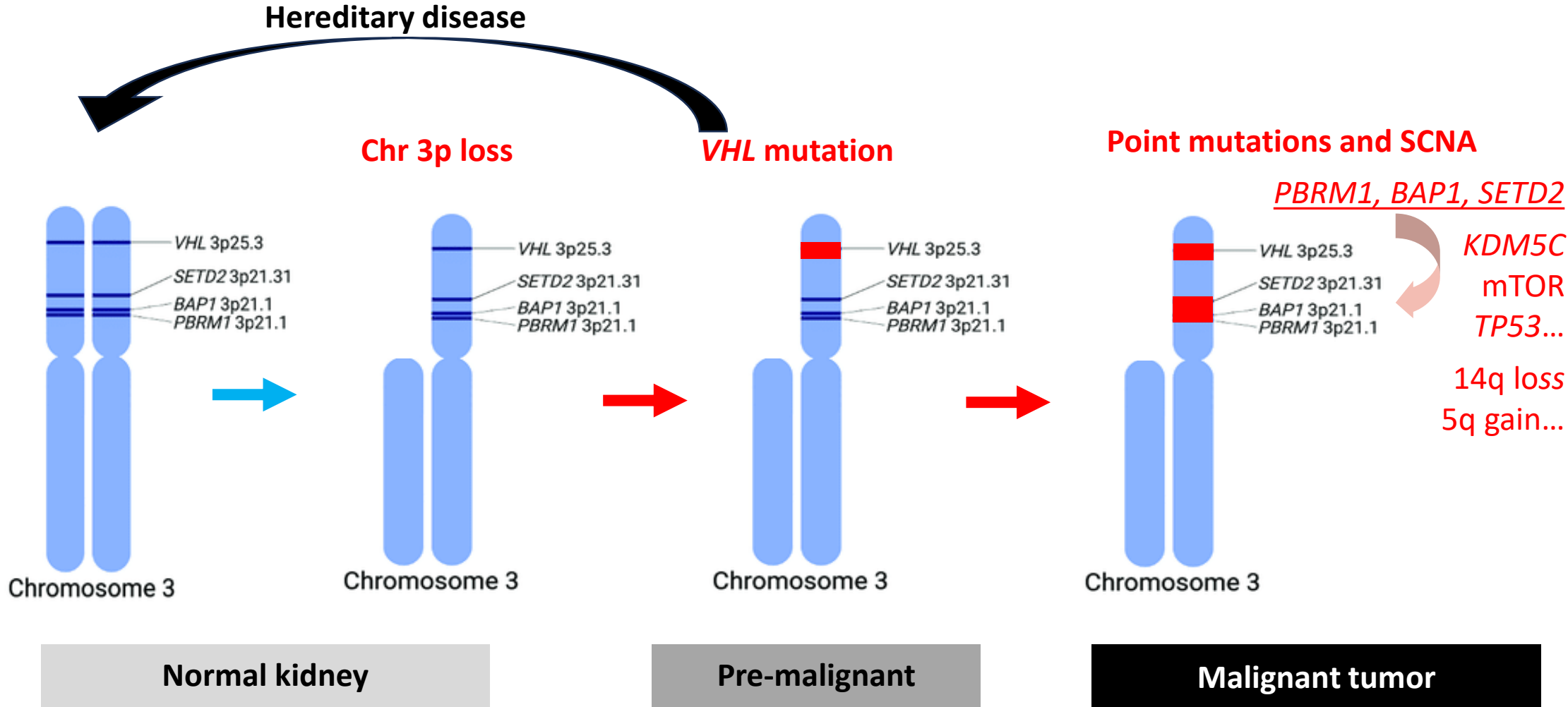
➤ *Vhl* loss alone: no tumors in murine models (*Bap1*, *Pbrm1*)

➤ Amplification of HIF response by *PBRM1* loss

➤ Frequent chr. 14q loss (*HIF1A*)

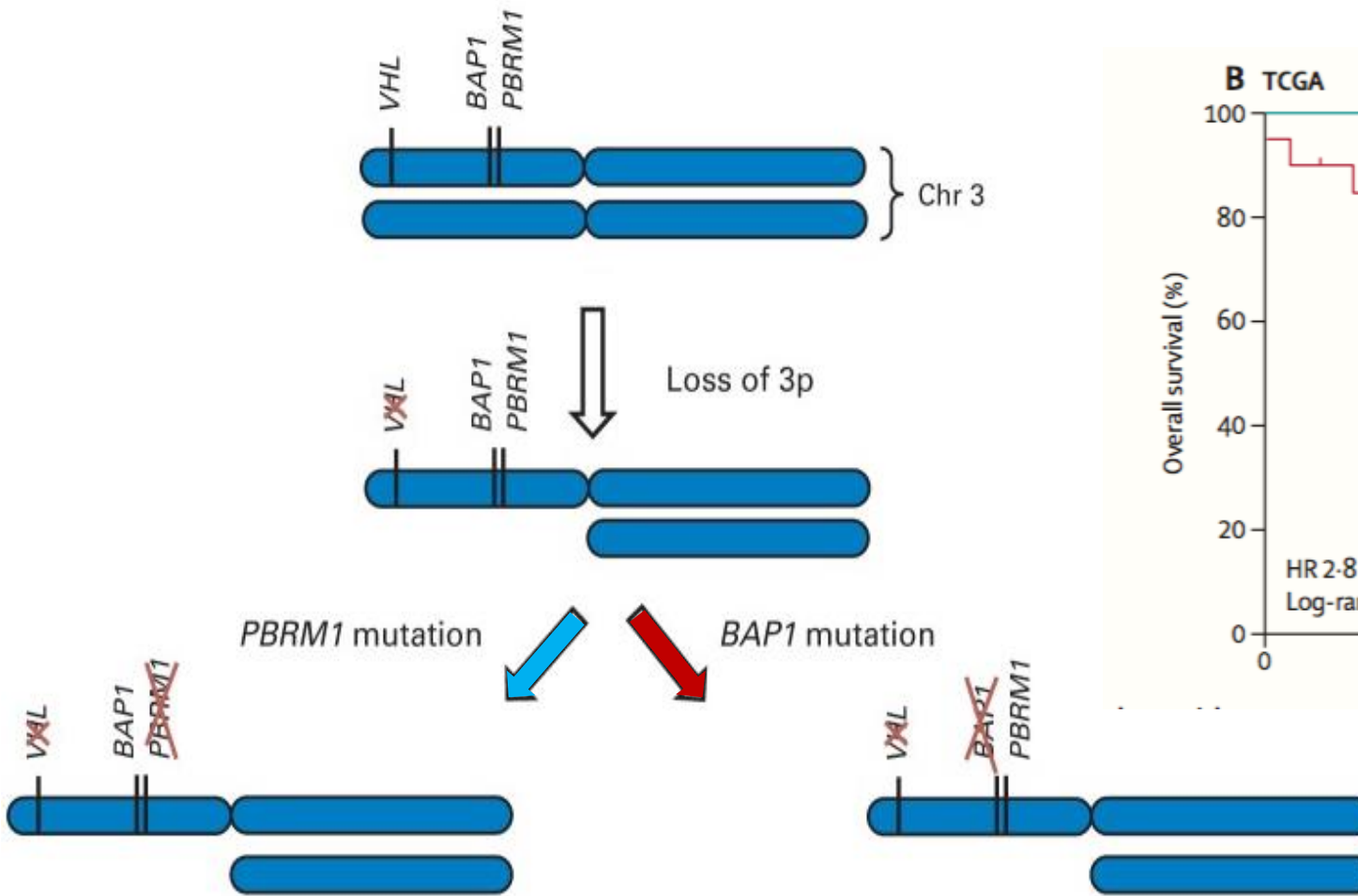
➤ Antitumor effects of HIF2α i (belzutifan; HIF-1α unaffected)

Clear cell RCC: sporadic tumor evolution



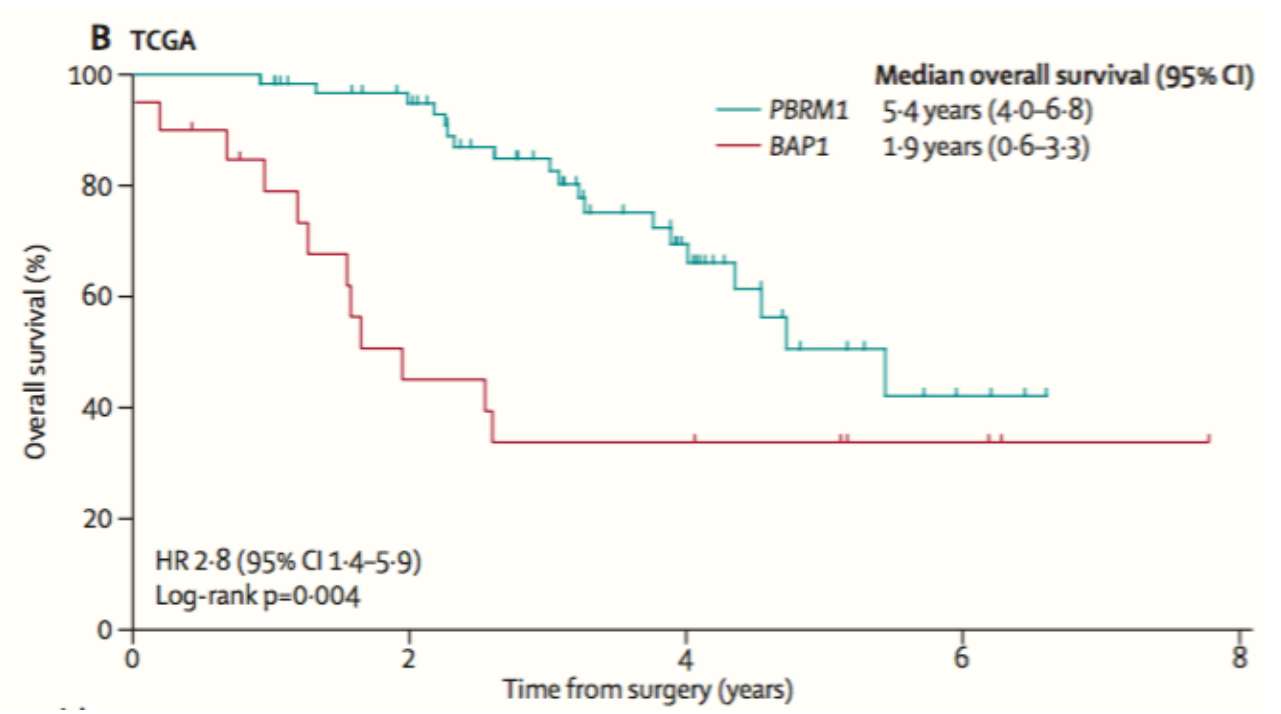
Turajlic, ESHG 2023 conference (new TRACERx study)

Chromatin remodellers are not randomly mutated: mutually exclusive *PBRM1* and *BAP1* mutations



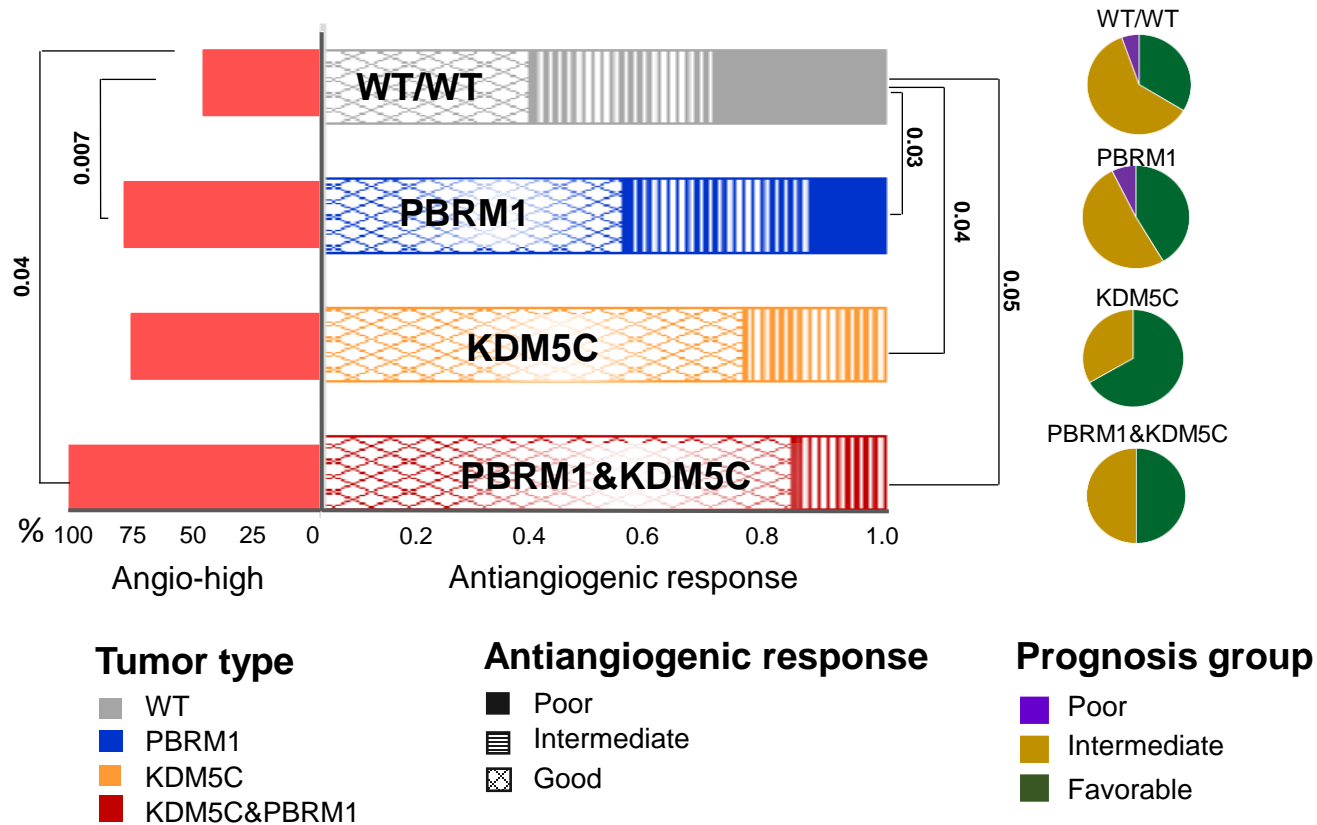
Low grade
Angiogenic

High grade
Inflamed

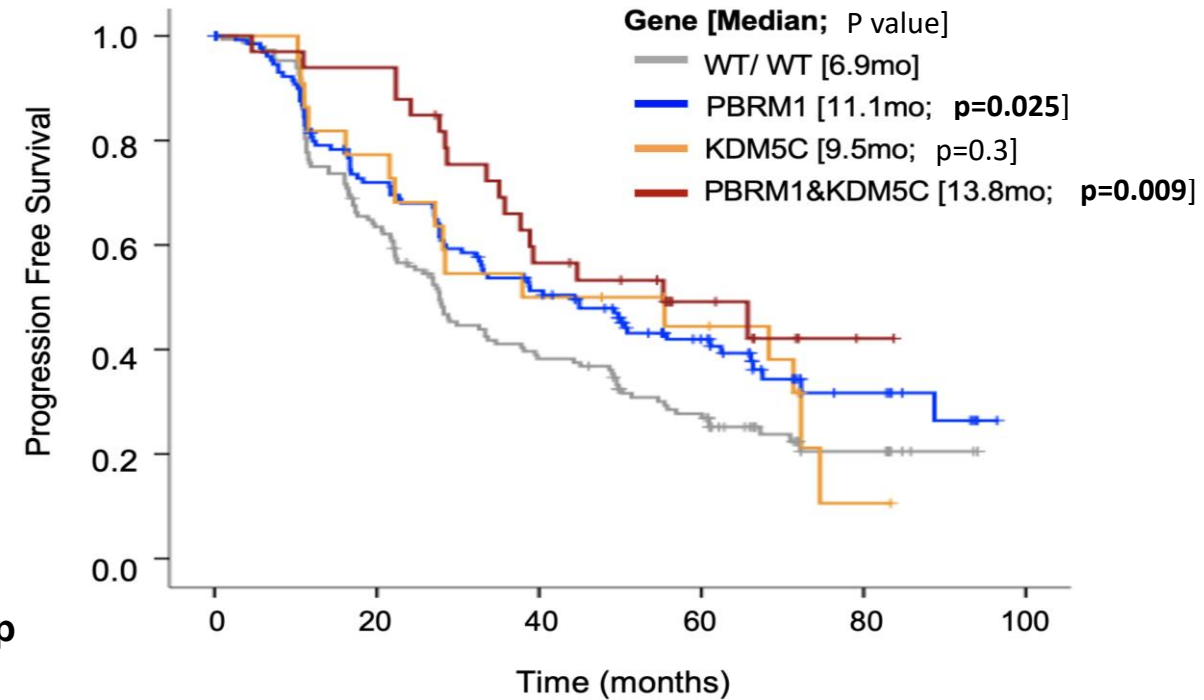


Chromatin remodellers are not randomly mutated: co-occurrence of *PBRM1* and *KDM5C* mutations

Spanish Discovery (n=155) **Sunitinib**



IMmotion151 Validation (n=343) **Sunitinib**



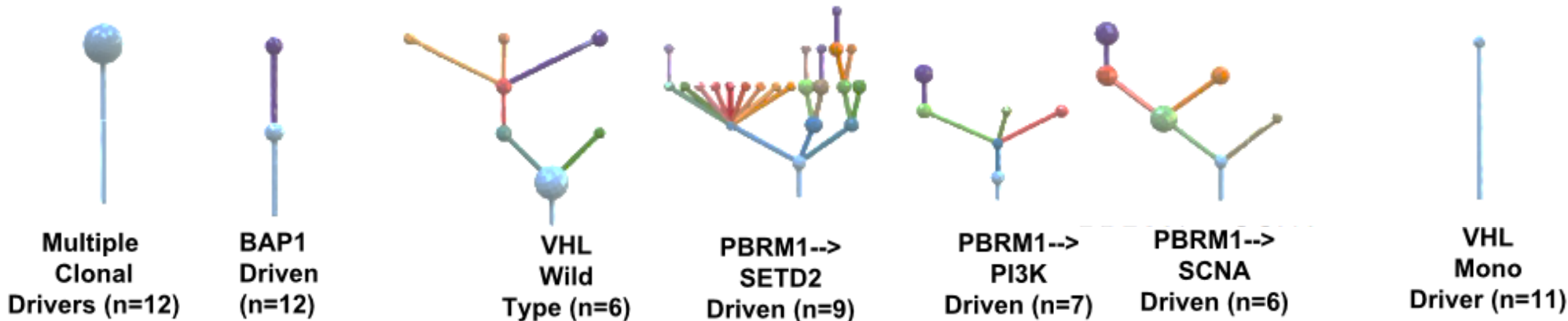
Different tumor evolution trajectories: intratumor heterogeneity

TRACER_X

7 evolutionary subtypes

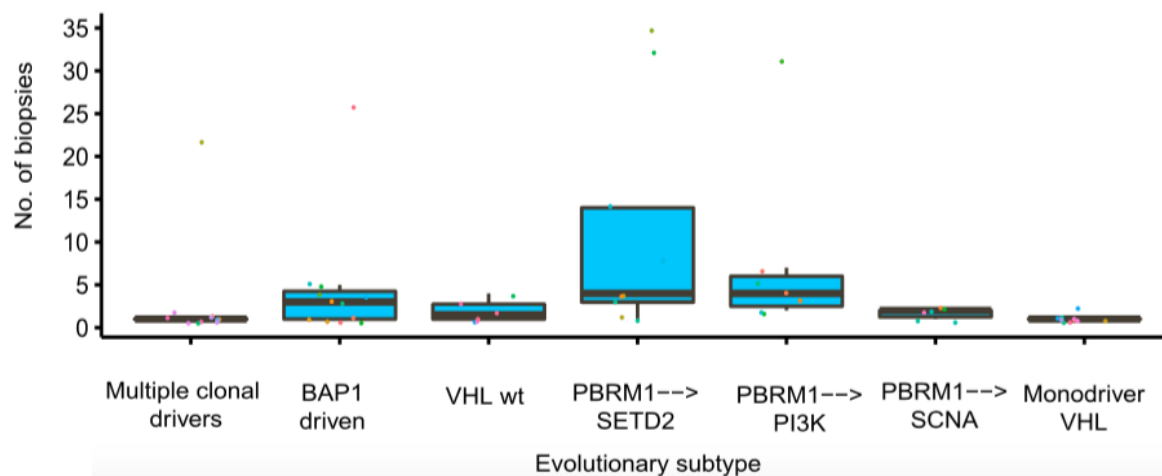
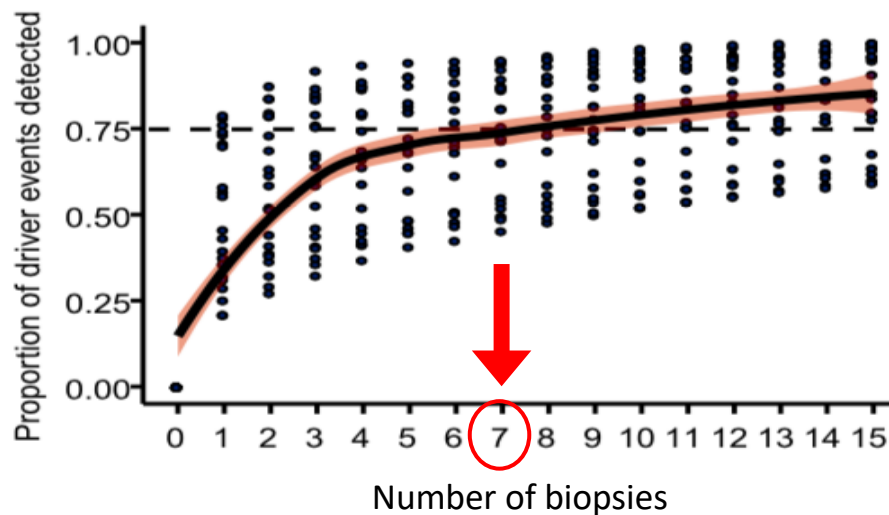
Rapid progression

Attenuated progression



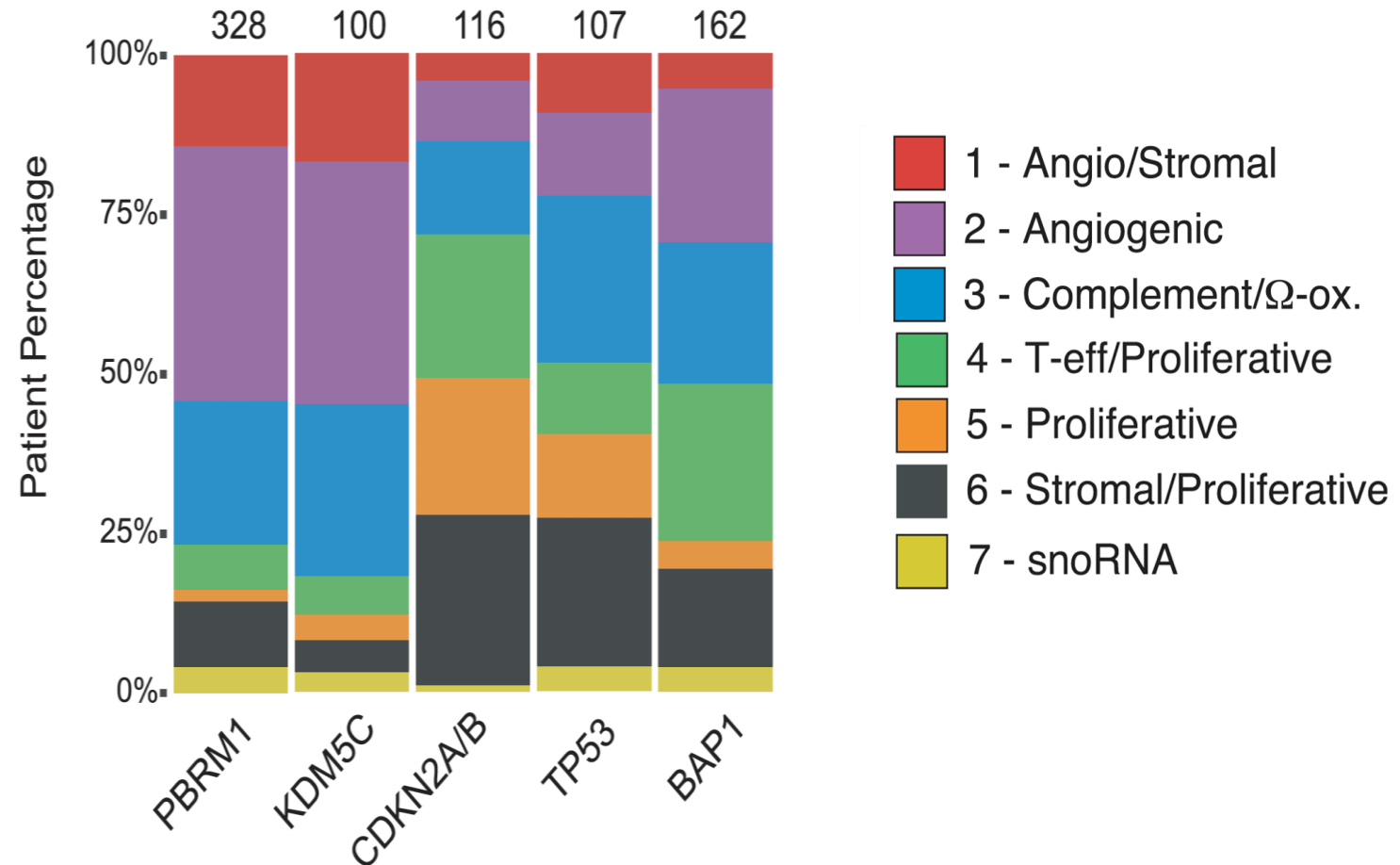
7 biopsies to detect 75% of mutations

To detect 75% of mutations



Mutations and gene expression signatures are connected

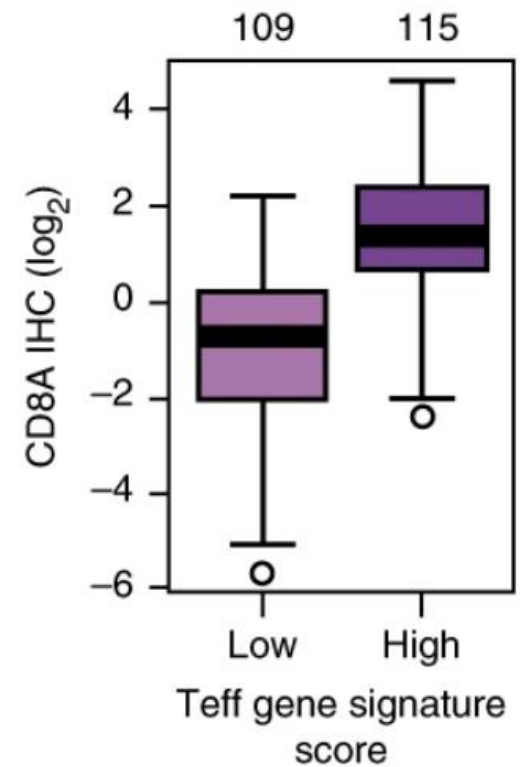
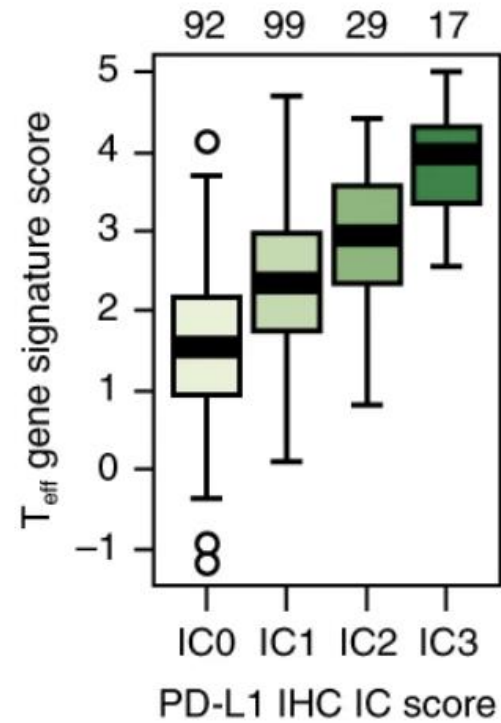
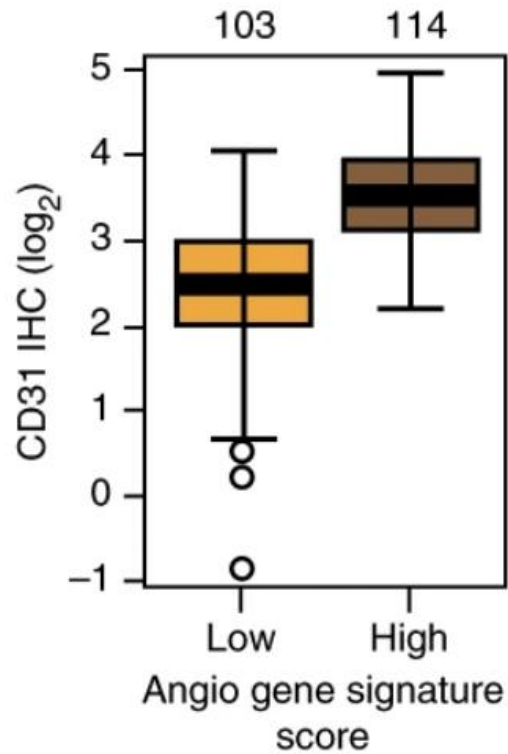
Molecular subtypes of ccRCC by RNAseq



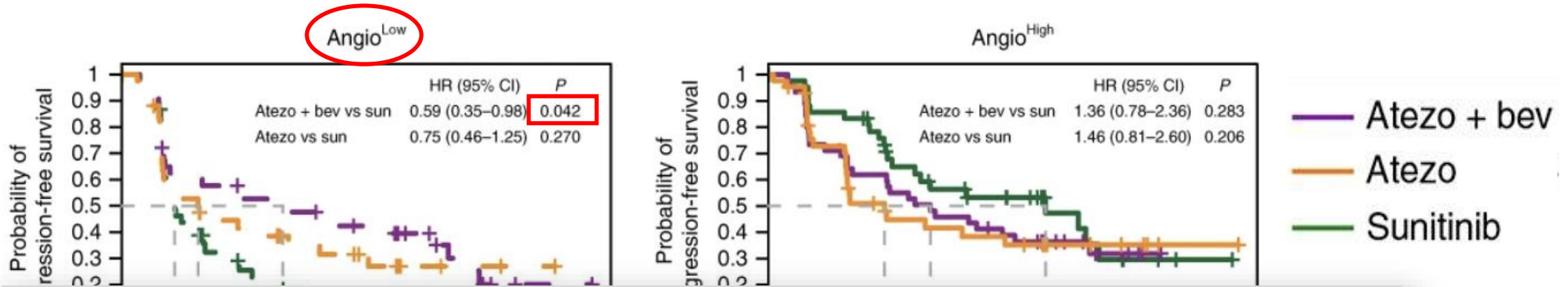
Gene mRNA signatures accurately associate with tumor characteristics

Angiogenesis: *VEGFA, KDR, ESM1, PECAM1, ANGPTL4, CD34*

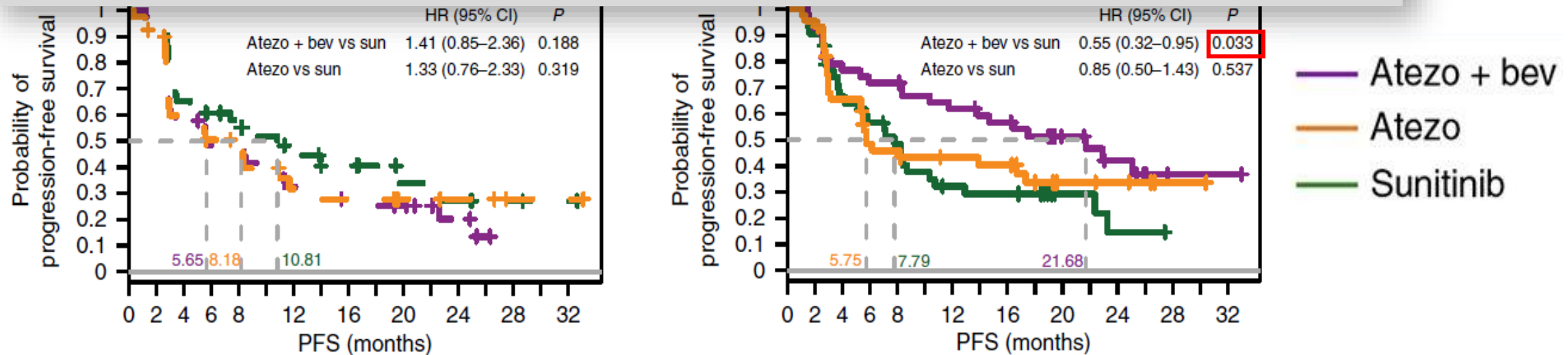
T-effector: *CD8A, EOMES, PRF1, IFNG, CD274*



Gene mRNA signatures associate with immunotherapy/ antinangiogenic response

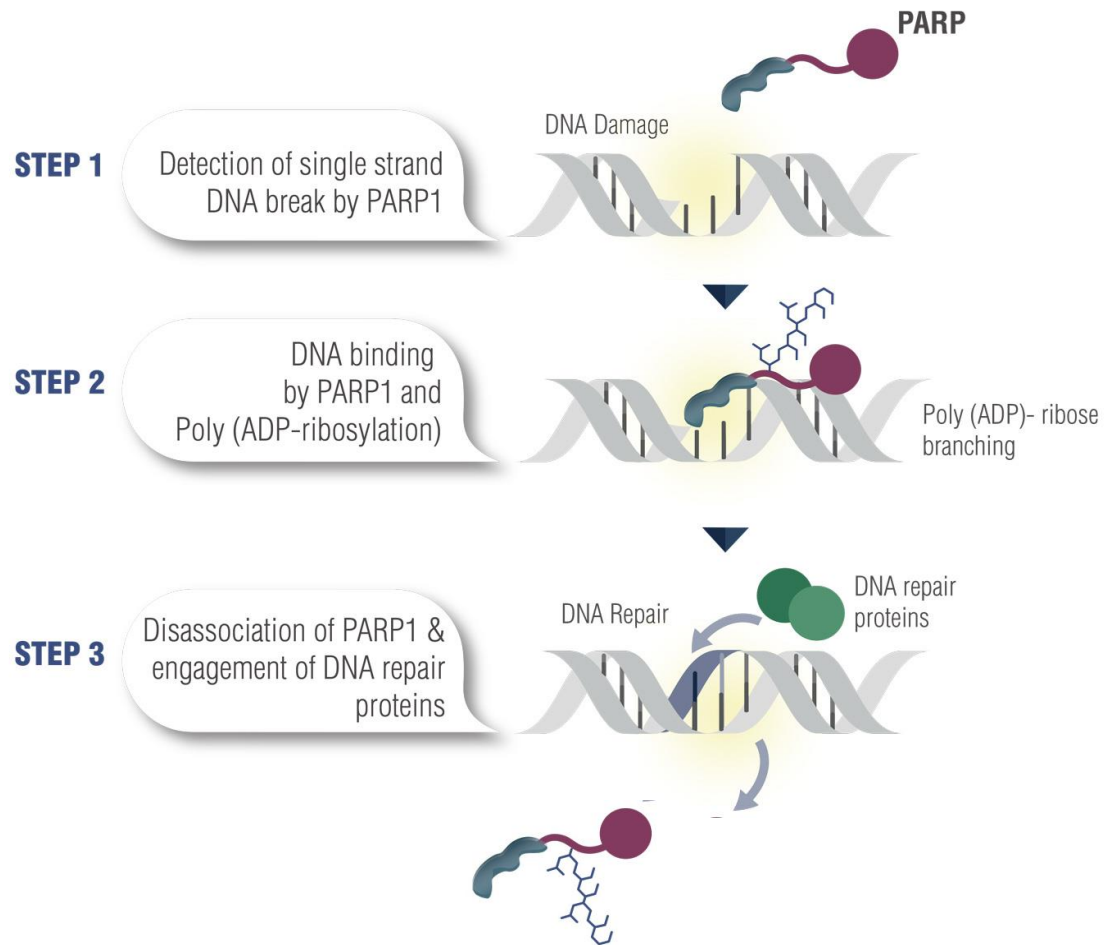


However, gene mRNA signatures reflect tumor microenvironment, not the tumor cell



However, more intrinsic factors associated with drug sensitivity?

PARP1 mediates DNA repair



- **Low expression of *PARP1* in tumors** leads to less efficient repair of DNA damage, higher immune infiltration, stromal and immune checkpoint genes scores and neoantigens expression
- **Inhibitors of PARP have a synergistic effect with antiangiogenics** (olaparib plus bevacizumab in ovarian cancer; *NEJM 2019 381:2416*)

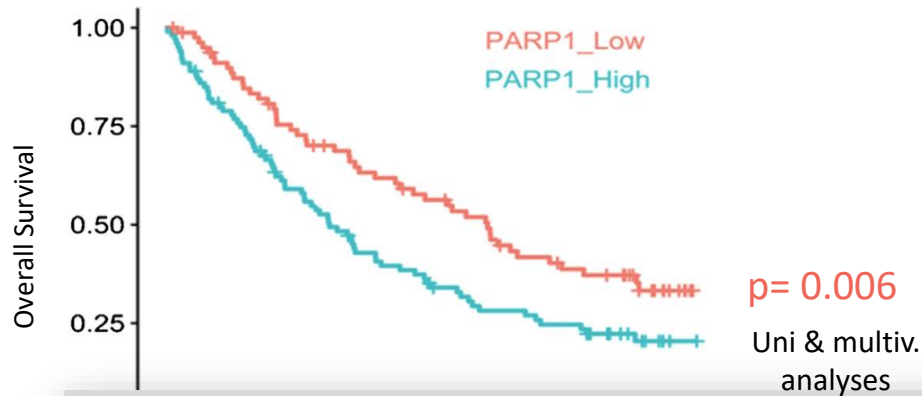
Does tumor *PARP1* expression in ccRCC modify drug sensitivity?

- Immunotherapy
- Antiangiogenics

PARP1 expression modulates drug response interacting with PBRM1 mutation

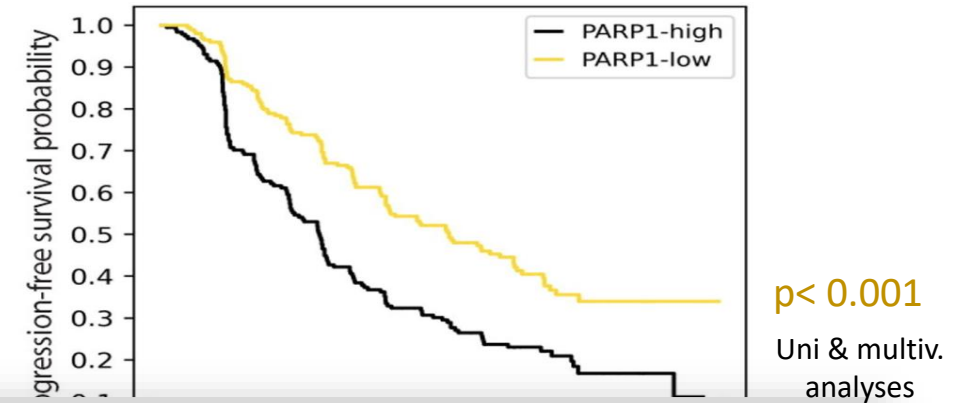
Hawinara, Eur Urol 2022, 81:145

Nivolumab

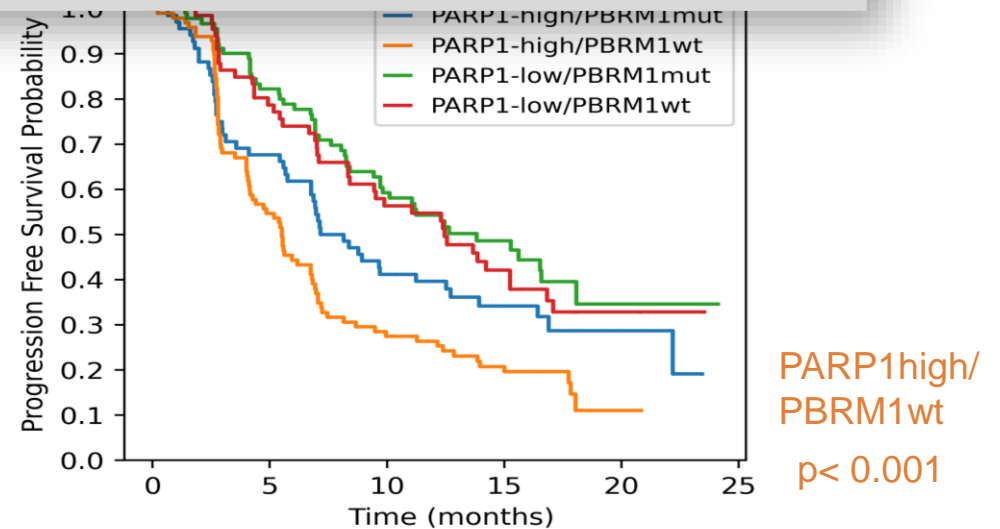
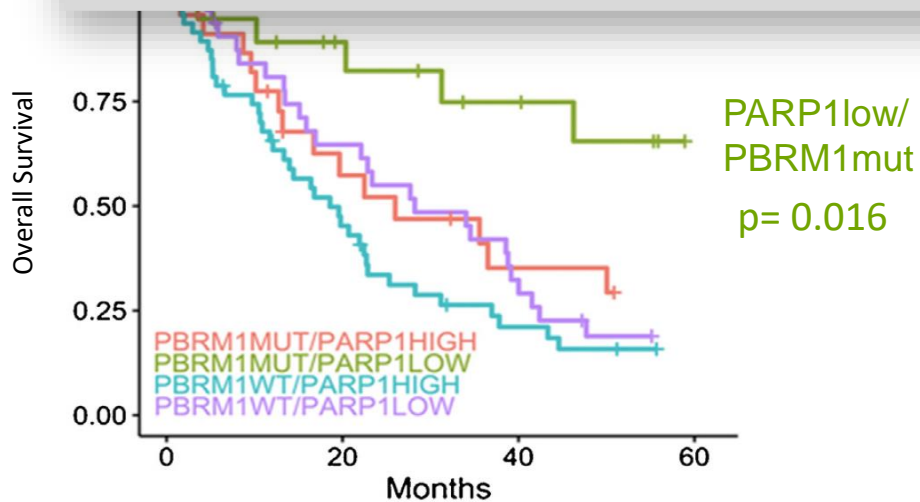


Eur Urol 2022, 82:334

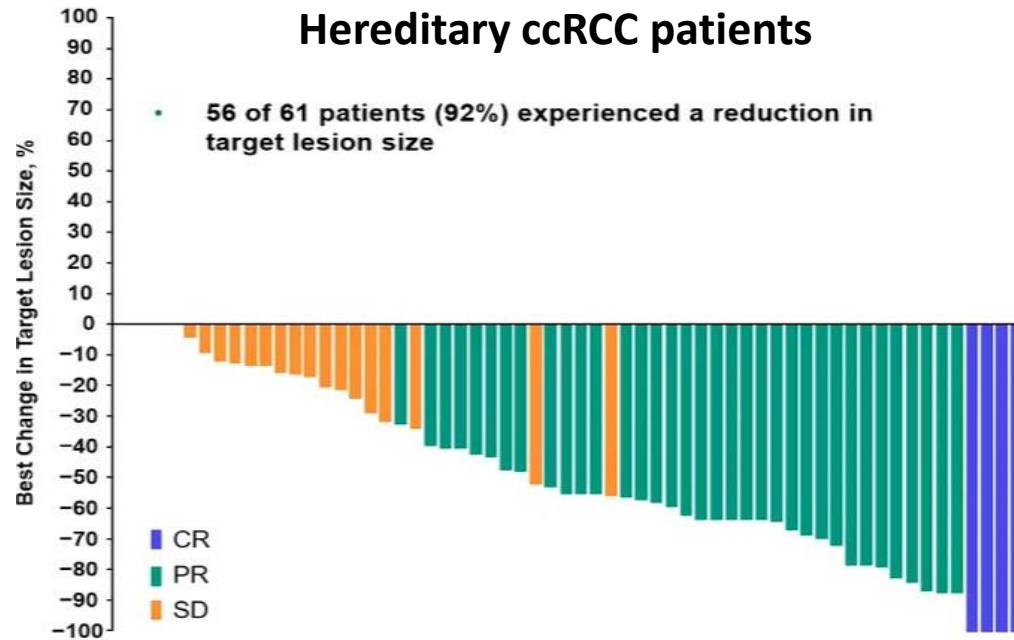
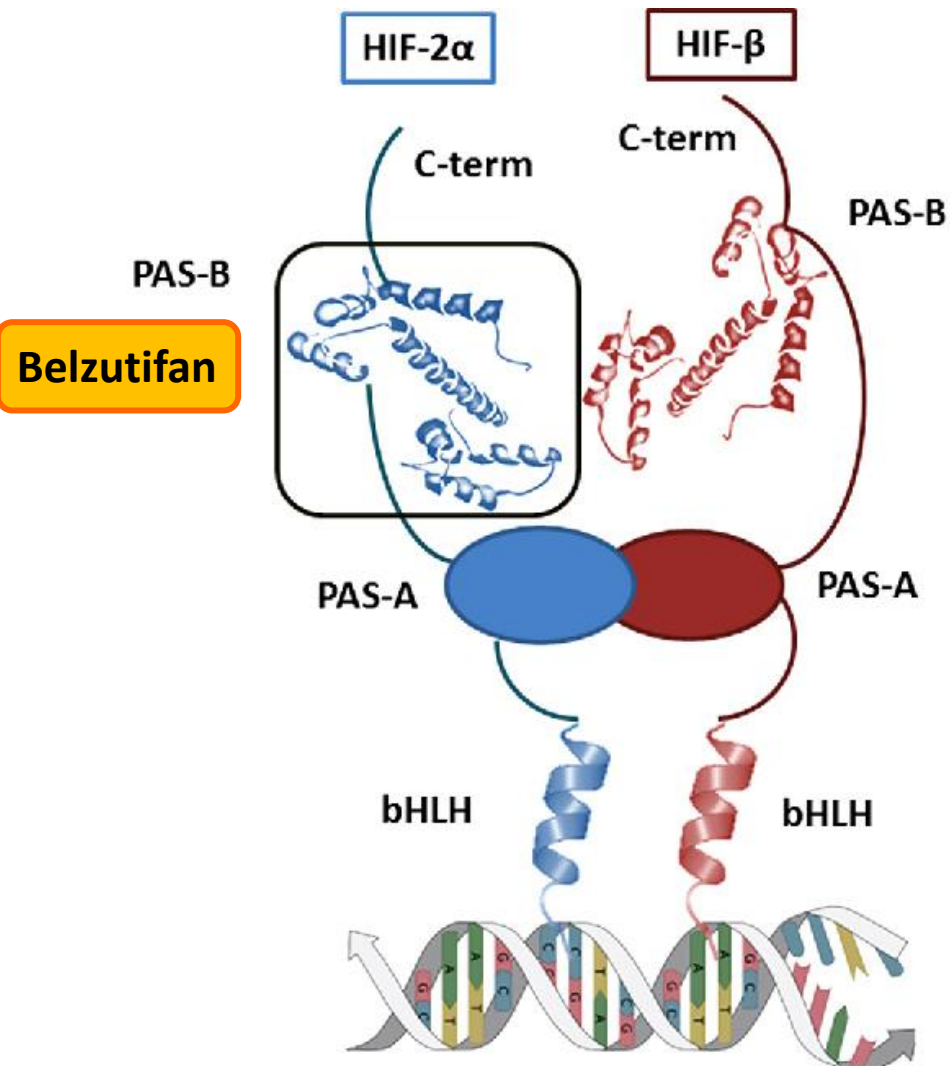
Sunitinib



However, the underlying mechanisms still under investigation



HIF2a inhibitor (belzutifan) in ccRCC



VHL disease ccRCC

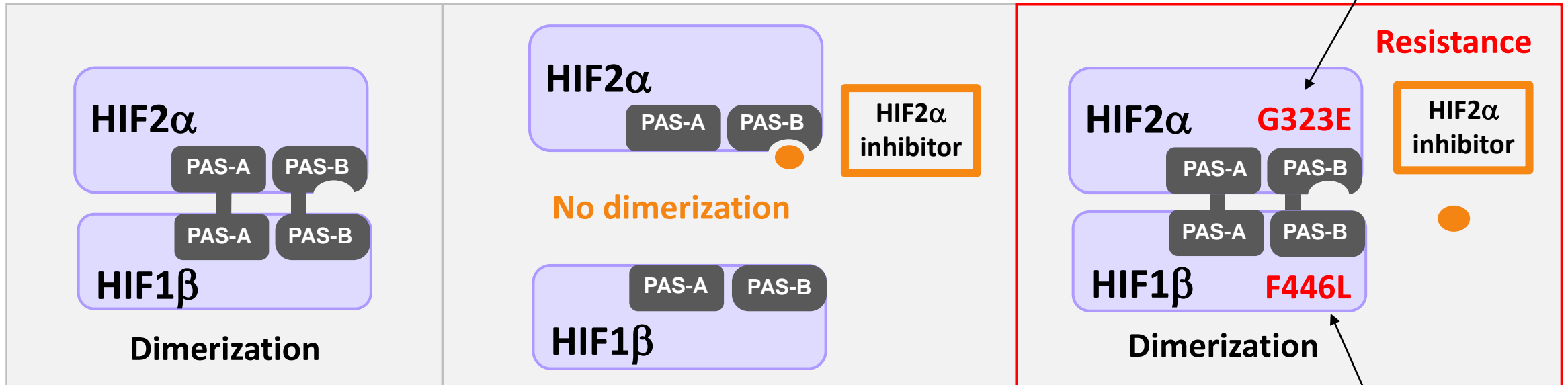
- *VHL* mutated germline
- Surveillance
- Primary tumors <3 cm
- No metastasis

Sporadic ccRCC

- *VHL* mutated somatically
- Metastatic tumors
- Greater molec. heterogeneity
- Response?

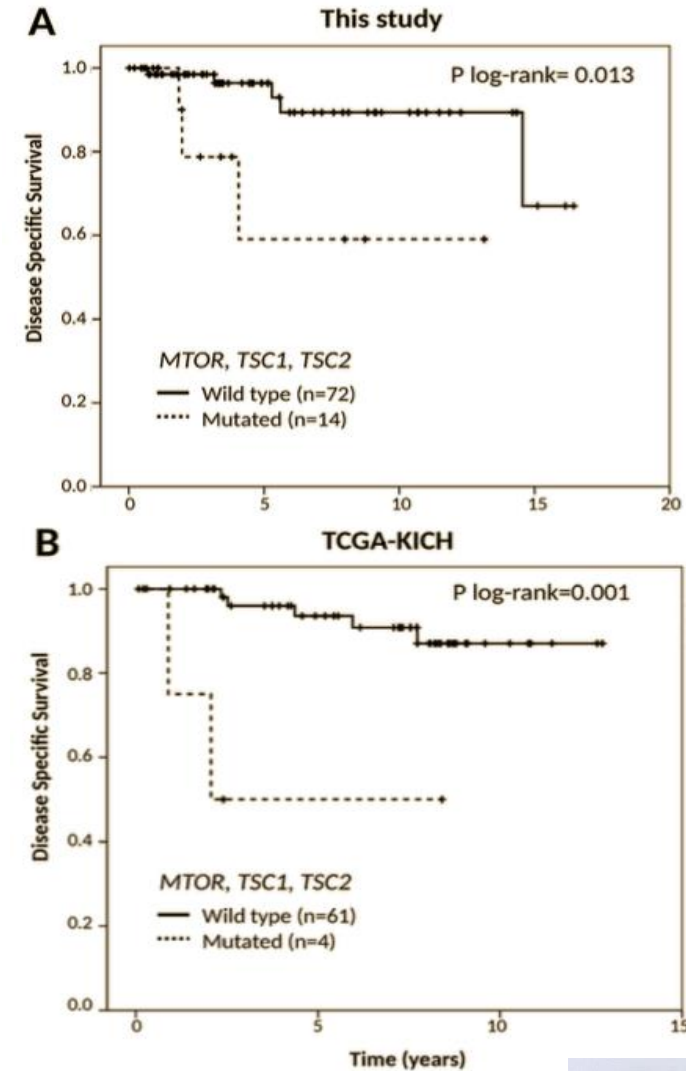
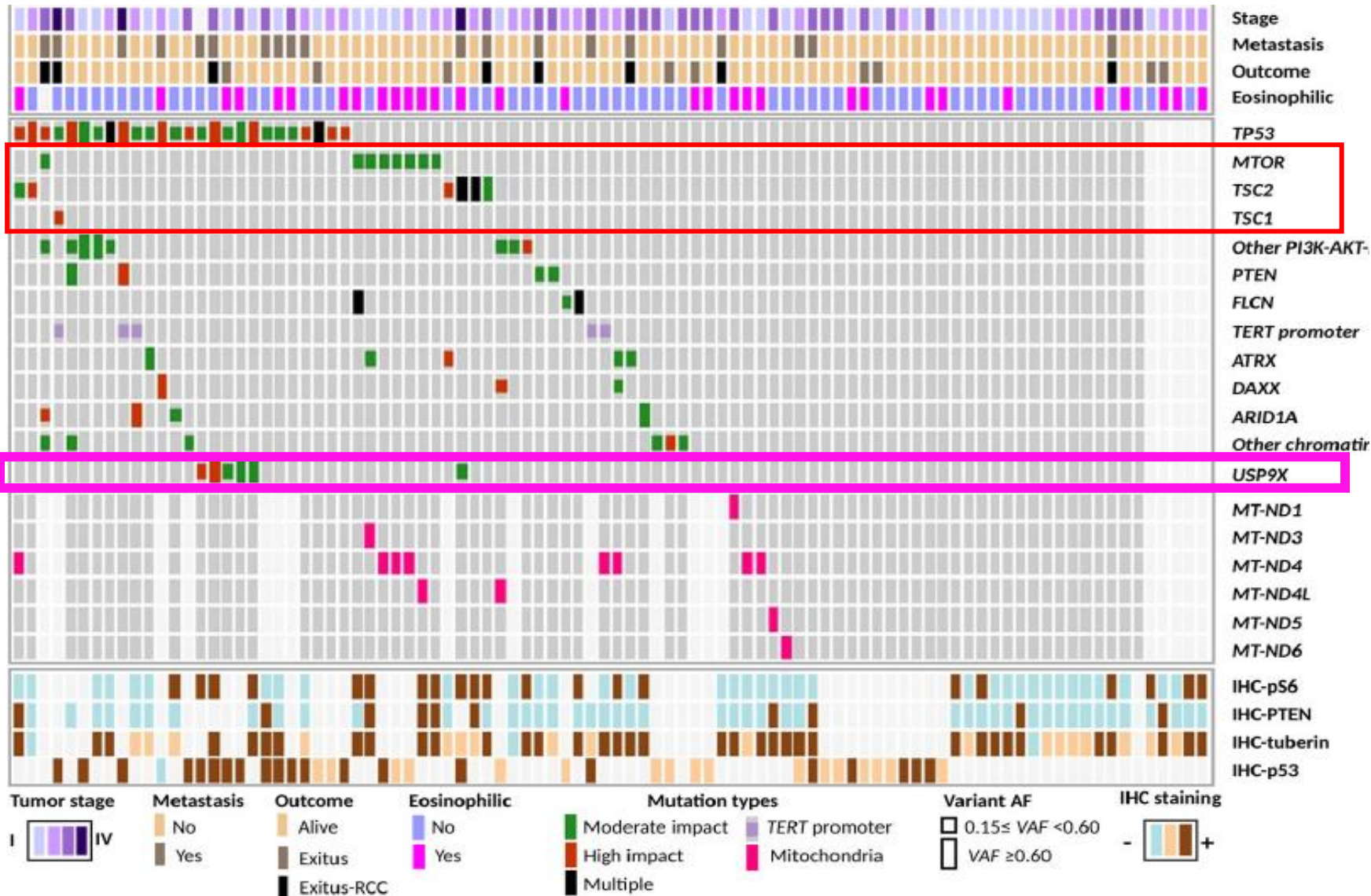
Belzutifan resistance mechanisms

- Phase I trial PT2835 in advanced/metastatic ccRCC (2 patients)



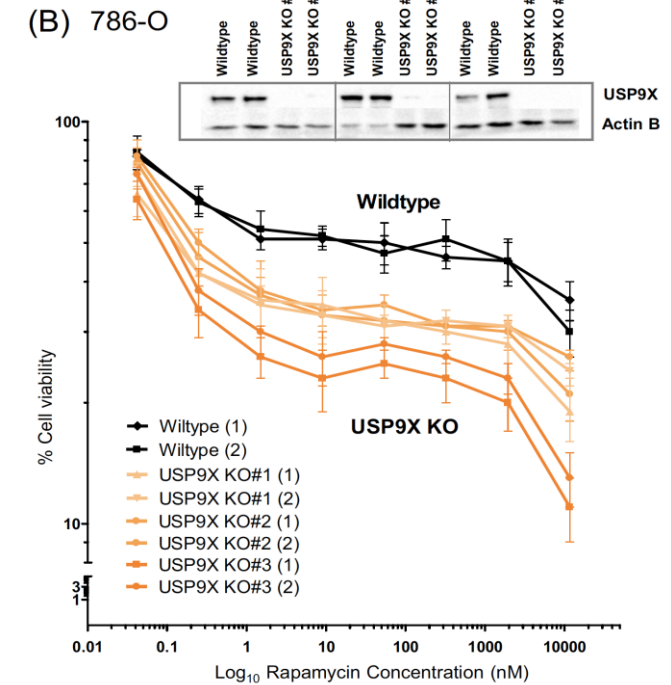
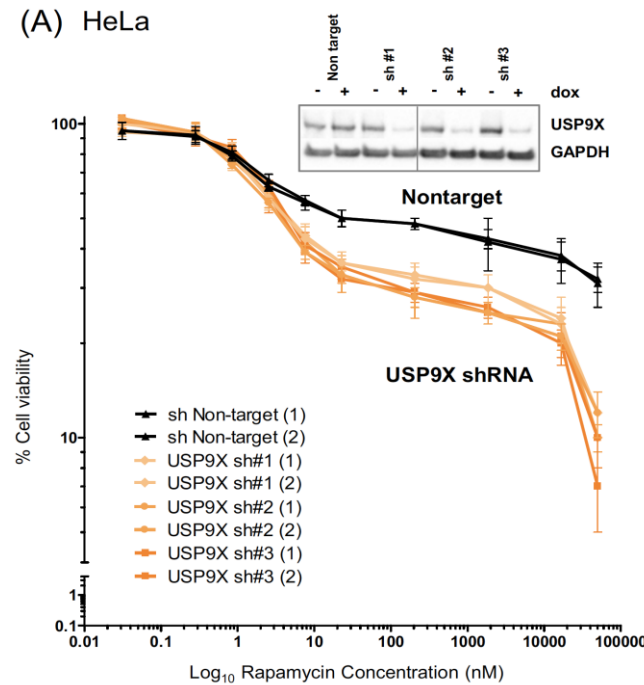
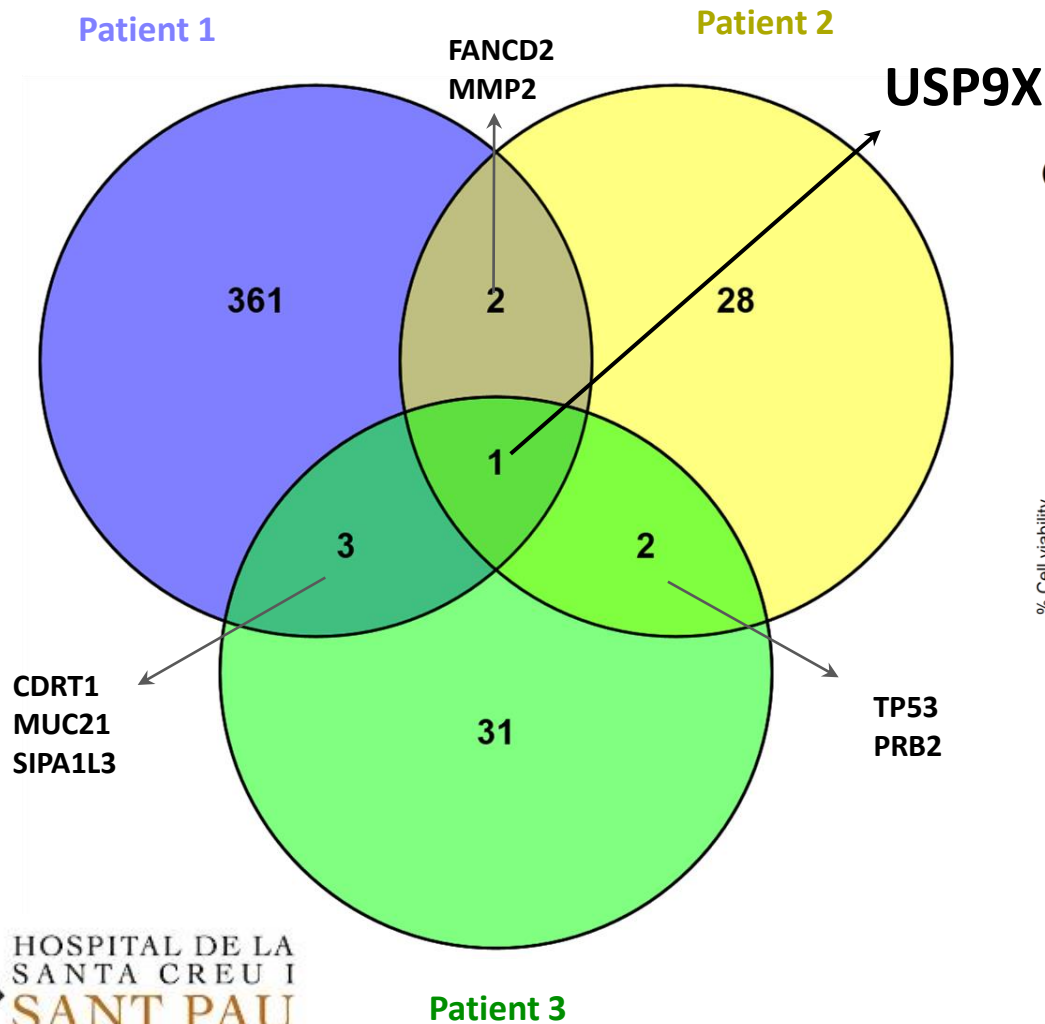
- Preclinical tumorgraft model

mTOR pathway alteration in chromophobe RCC confers poor prognosis

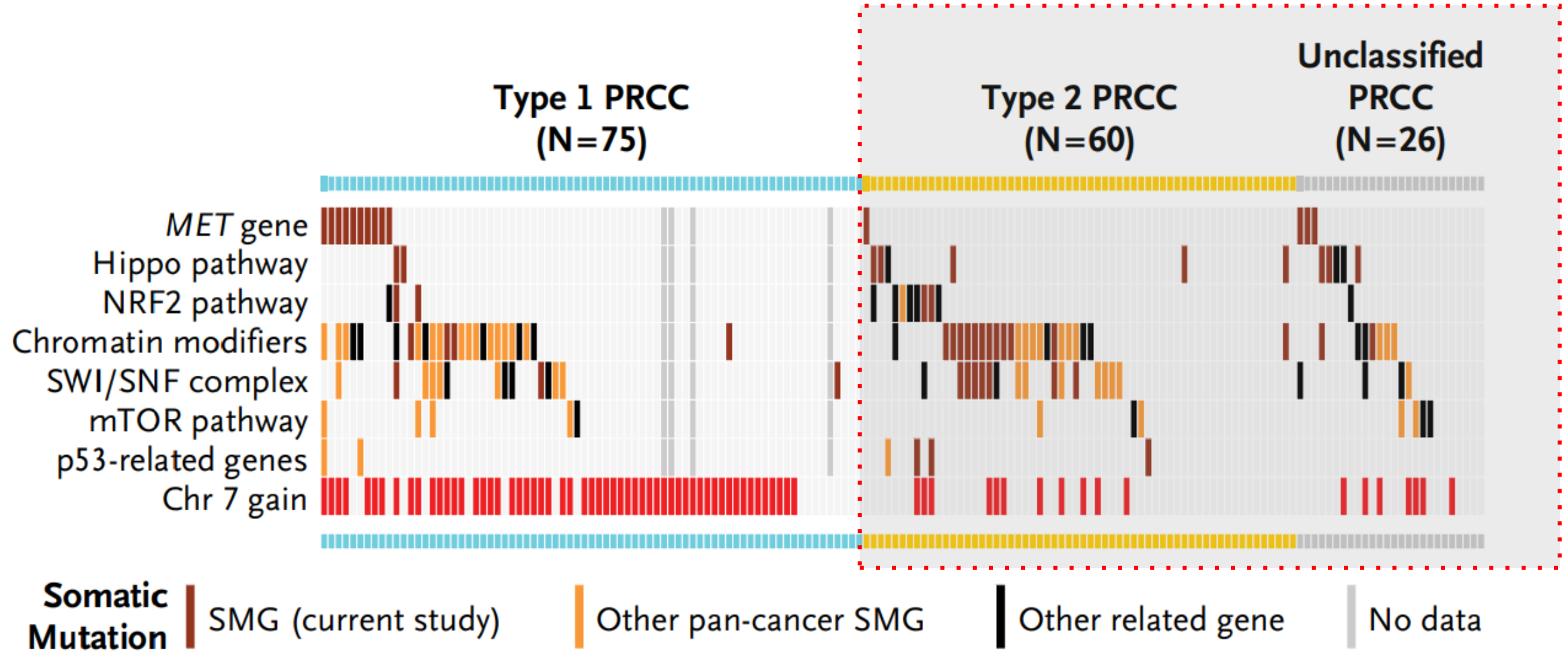


USP9X is a novel marker for mTOR inhibitor response

Whole Exome Sequencing of 3 chRCC patients with extraordinary response to temsirolimus



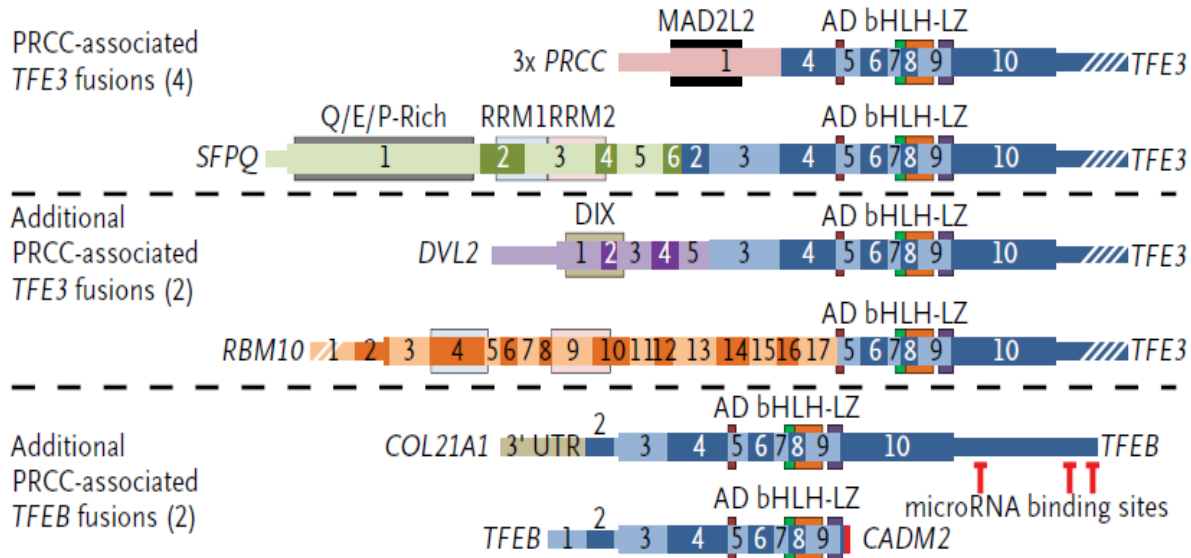
“Papillary” RCC



“Papillary” RCC

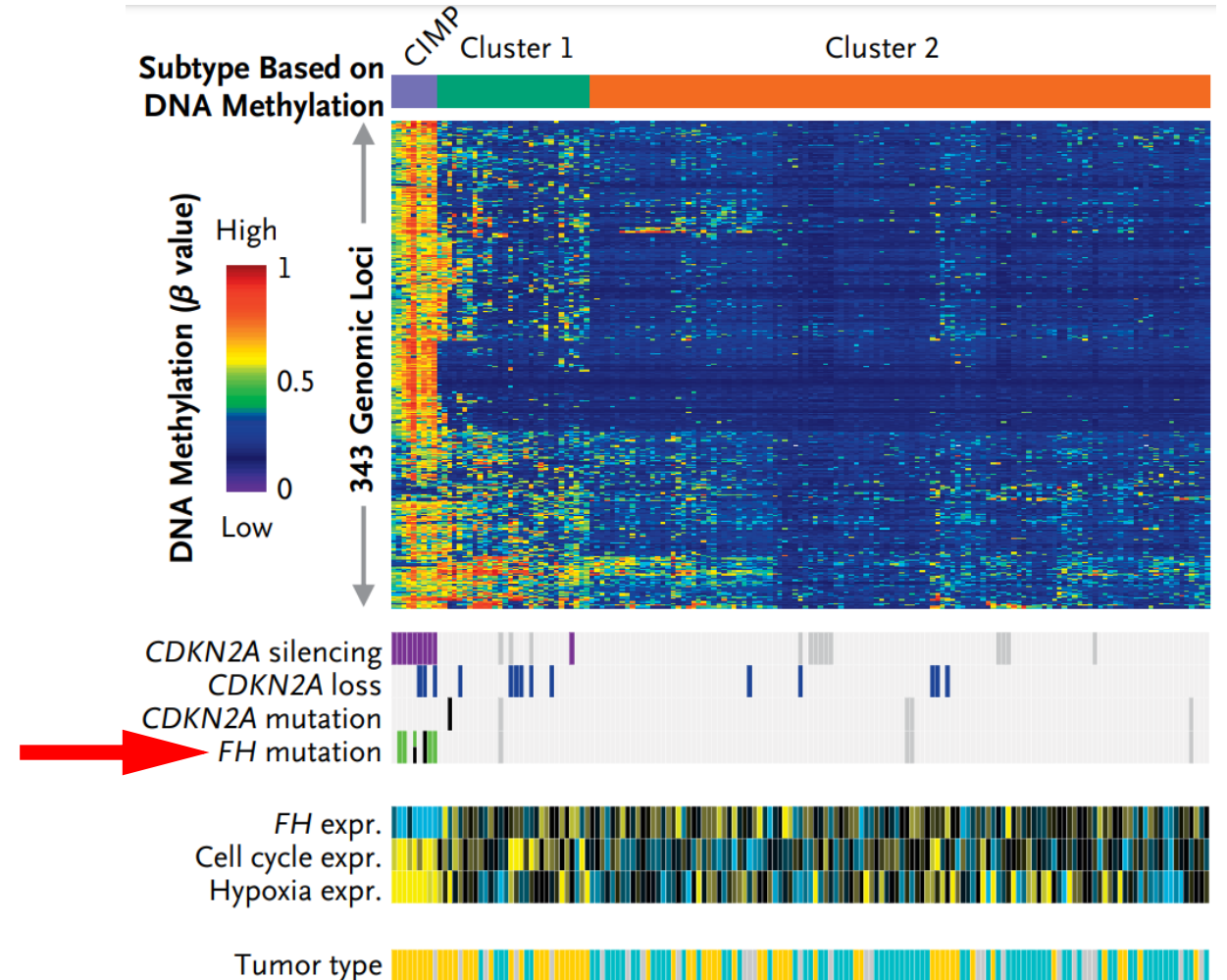
Translocation RCCs

(12%, 7 of 60 “type 2” tumors)

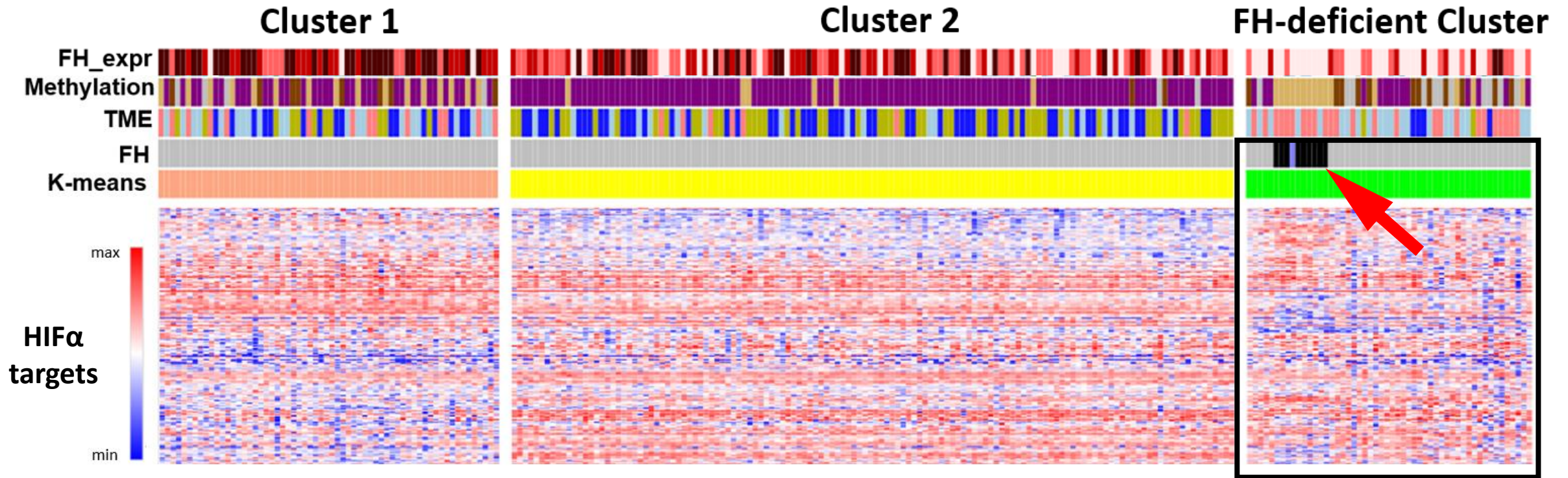


FH-deficient RCC

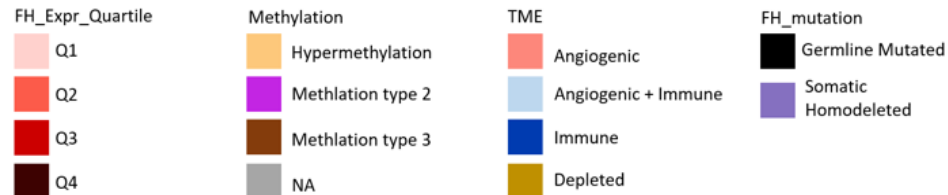
(8%, 5 of 60 “type 2” tumors)



Papillary RCC tumors with different transcriptomic HIFa profiles

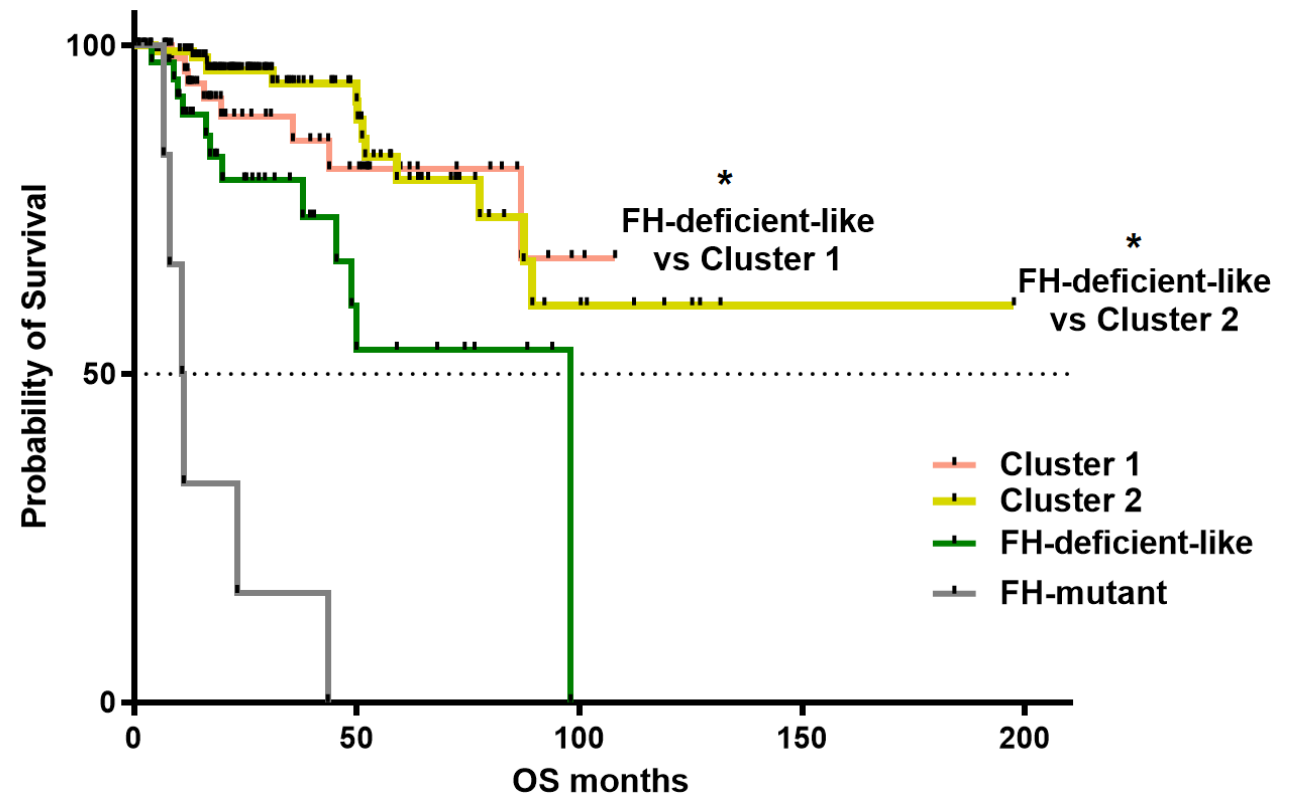
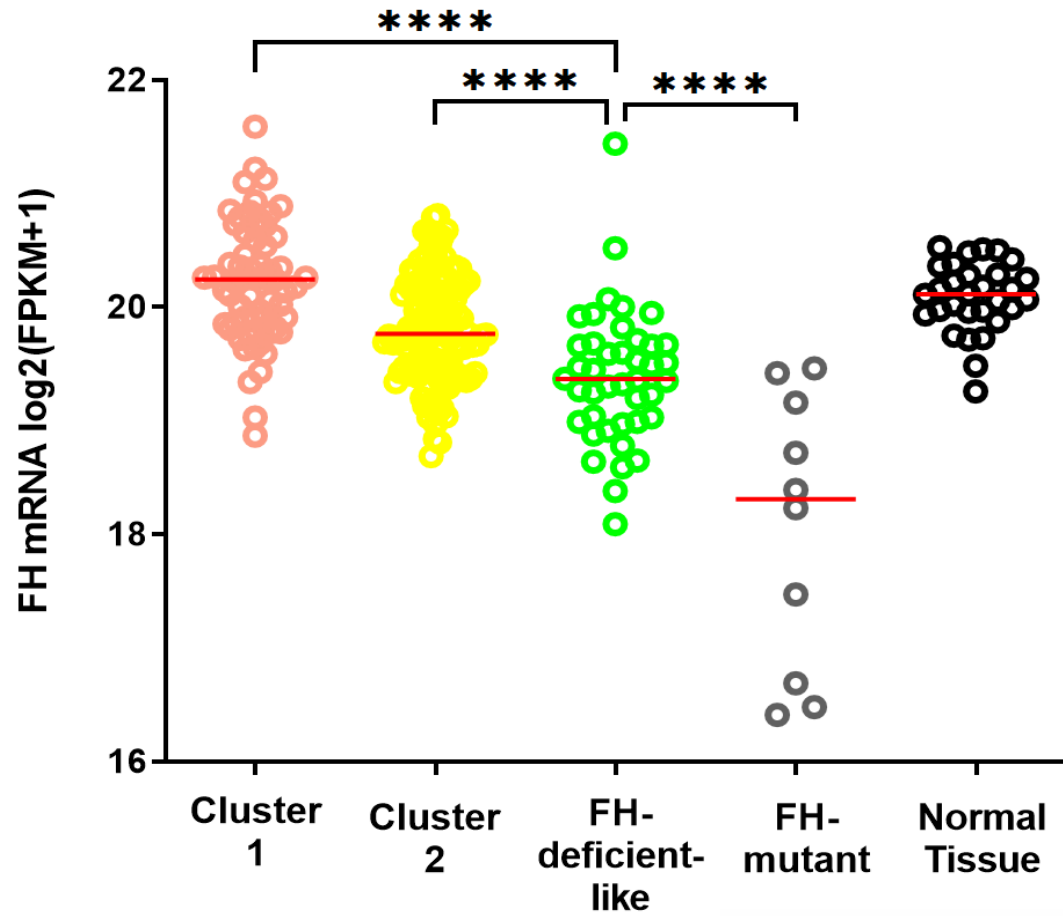


Tumors with known driver mutations removed



Javier de Nicolás-Hernandez

Transcriptomic identification of novel “FH-deficient like” papillary RCC subtype



Relevance for treatment selection?

Conclusions

- VHL inactivation is the homogenous driver of ccRCC, through HIF2-alpha accumulation. However, VHL needs to be complemented with secondary alterations
- Mutations in genes encoding chromatin remodelers (e.g. *PBRM1*, *BAP1*, *KDM5C*) modulate TMA and impact drug response. In some cases, interacting with other genes (e.g. *PARP1*). Still no biomarker in the clinic
- ITH remains a challenge in ccRCC. Novel techniques such as scRNAseq, may aid in this respect
- Non-ccRCC research lags behind, we need genomic studies that can provide a more in-depth molecular classification tumor with a clinical meaning

Acknowledgments



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Epithelial Carcinogenesis Group (**FX. Real**)

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Benoit Beuselinck



Pablo Maroto
Georgia Anguera



Guillermo de Velasco
Daniel Castellano, Luis Robles



Javier Puente
Natalia Vidal



Ignacio Duran



Nuria Lainez