#24P - Chromosome 3p-related gene alterations (GA) as biomarkers for immunocombinations in metastatic renal cell carcinoma (mRCC): a hypothesis-generating analysis

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Background

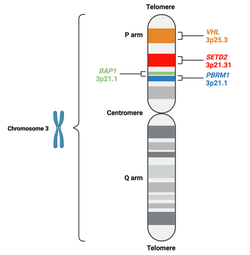

Figure 1. *Representation of chromosome 3p genes (between the 3p25 and 3p21 segments).*

Identifying biomarkers for mRCC is an unmet need in actual immunotherapy (IO) era[1]. Available data regarding chromosome 3p-related genes (*i.e., VHL, PBRM1, SETD2*) (*Figure 1*) as potential predictors for therapy response is conflicting[1-4].

We describe the correlation of these GA with clinical outcomes in mRCC patients (pts) treated with IO/IO or IO/tyrosine kinase inhibitor (TKI).

Methods

We performed a single-center retrospective analysis on mRCC pts treated with first line IO/IO or IO/TKI. A multi-gene panel was used, allowing the amplification of 841 amplicons (54.93kb, human reference sequence hg19/GRCh37) in the coding sequences of the following genes: *ATM, BAP1, KDM5C, MET, MTOR, NF2, PBRM1, PIK3CA, PTEN, SETD2, SMARCB1, TP53, TSC1, TSC2, VHL*.

Conclusions

Our data shows a possible negative predictive role of *SETD2* GA for IO-based therapy in RCC. Concomitant *VHL* and *PBRM1* mutations could act as a predictor for IO/TKI efficacy.
Our hypothesis-generating analysis highlights the need of an integrated evaluation of these genes as promising biomarkers in RCC. Further larger studies are required.

References: **1**. Rosellini M et al. Prognostic and predictive biomarkers for immunotherapy in advanced renal cell carcinoma. *Nat Rev Urol*. 2023;20(3):133-157; **2**. Miao D et al. Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma. *Science*. 2018;359(6377):801-806; **3**. Braun DA et al. Clinical Validation of PBRM1 Alterations as a Marker of Immune Checkpoint Inhibitor Response in Renal Cell Carcinoma. *JAMA Oncol*. 2019;5(11):1631-1633; **4**. Lu M et al. Pan-cancer analysis of SETD2 mutation and its association with the efficacy of immunotherapy. *NPJ Precis Oncol*. 2021;5(1):51.

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Results

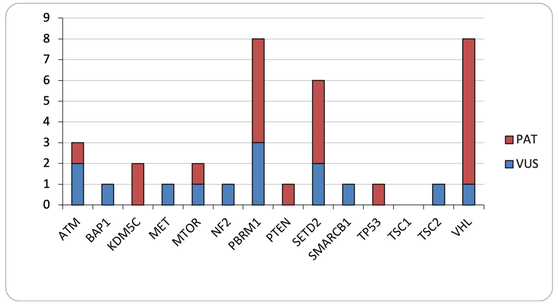

Figure 2. *Mutational frequency for each gene studied in our exploratory analysis. Abbreviations: PAT, pathogenic mutation; VUS, variant of unknown significance.*

• 30 mRCC pts undergoing IO/IO and IO/TKI were included. Of these, 18 had tumor tissue adequate for molecular analysis: 77.8% male, 22.2% female. Histology was 100% clear cell. IMDC risk was 50% intermediate, 33.4% good, 16.6% poor. First line therapy was 89% IO/TKI, 11% IO/IO.

• 83.3% pts (n=15) carried GA, among which 61.1% had a known pathogenic mutation (PAT) (*Figure 2*). Most common GA included *VHL* in 44% (n=8; 7 PAT and 1 variant of unknown significance - VUS), *PBRM1* in 44% (n=8; 5 PAT and 3 VUS) and *SETD2* in 33% (n=6; 4 PAT and 2 VUS).

• With the limit of a small sample that did not allow proper statistical analyses, *SETD2* mutated pts had lower median progression free (mPFS) and overall survival (mOS) than non-*SETD2* mutated pts. Higher mPFS and mOS were shown with *VHL* or *PBRM1* GA, especially in *PBRM1+VHL* mutated pts (*Table 1*). Of note, all *PBRM1+VHL* mutated pts underwent IO/TKI.

Gene	mOS		mPFS		Best response as (n. of pts)			
	Mut	Non-mut	Mut	Non-mut	CR	PR	SD	PD
SETD2	12	14.5	15	16	0	4	0	2
VHL	19	11	20	14	0	6	1	1
PBRM1	19	7.5	20	13	0	7	1	0
PBRM1+ VHL	20	7.5	20.5	13.5	0	4	1	0

Table 1*. Survival outcomes in mRCC patients carrying a chromosome 3p-related gene mutation compared with non-mutated patients, and their radiological response evaluation. Abbreviations: mPFS, median progression-free survival; mOS, median overall survival; n° of pts, number of patients; mut, mutated; non-mut, non-mutated; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.*

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