Identification of actionable targets in chromophobe renal cell carcinoma detected by multiplatform molecular analysis

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Background:

- Chromophobe renal cell carcinoma (chRCC) is rare and infrequently metastasizes or recurs after definitive local therapy.
- We performed multiplatform tumor profiling to identify potentially druggable targets in chRCC.

Methods:

- 12 cases were identified from 65,000+ tumors submitted for commercial testing at Caris Life Sciences. All tissues were internally reviewed by a dedicated pathologist to confirm diagnosis.
- IHC was performed on 19 proteins.
- FISH was performed on EGFR, HER2, and TOP2A.
- Targeted NGS (tNGS) was performed on 47 genes.

Results:

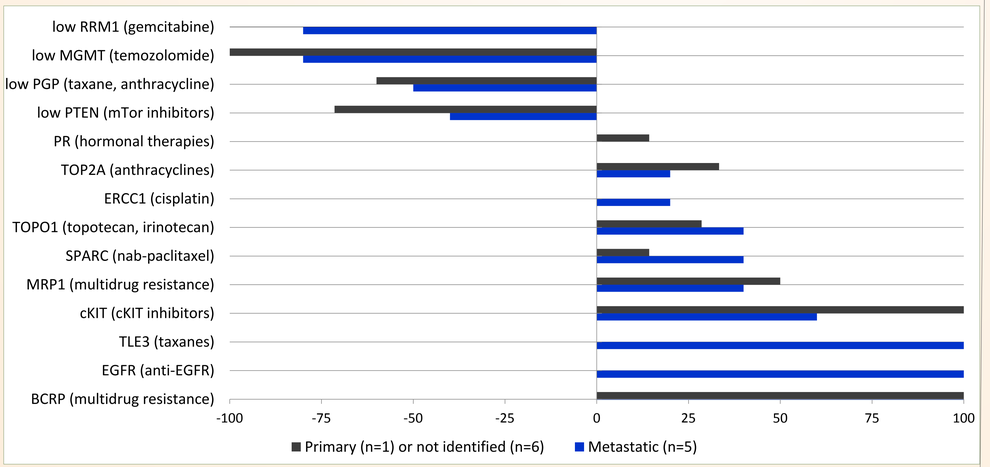
	Primary or not identified	Metastatic
No. patients	7 (1=primary)	5
Vital status	3 deceased 4 unknown	3 deceased 2 unknown
Gender	Female: 5 Male: 2	Male: 4 Female: 1
Median age	49	54
Med. age at time of CMI	46	55
Age range	37-67	54-64

Clinical information

Case #	History of Mets	Fuhrman grade	Sarcomatoid Features	Tumor size, mm	Tumor Necrosis	Stage
1	Yes	4	Present	170	Present	Pathologic 3aX M
2	Not provided	4	Not provided	Not provided	Not provided	Pathologic 3b XX
3	Yes - brain	3	Not provided	50	Present	Pathologic 1b XX
4	Yes - LN	3	Not provided	120	Present	Pathologic 4 1 X
5	No		Not identified	60	Present	Pathologic 3a X 0
6	Not provided	4	Present, 30%	155	Present	Pathologic 3a X X
7	Not provided	2	Not identified	145	Present	Pathologic 3a X X
8	Yes	3	Not provided	98	Present	Pathologic 3a 1 X
9	Yes	2	Not provided	111	Not provided	Pathologic 3a X 1
10	Not provided	4	Not identified	85	Present	Pathologic 2a X X
11	Not provided	4	Not identified	92	Not provided	Pathologic 2 X X
12	Not provided	4	Present, 80%	150	Present	Pathologic 3a X X

Immunohistochemistry

Either overexpression, reported as percent positive of total cases tested, or loss, reported as percent negative of total cases tested. Biomarkers tested with no identified aberrations include AR, ER, HER2, PDGFR, TS, and TUBB3.



**One case was evaluated for PD-1 tumor infiltrating lymphocytes and PD-L1 expression levels, with no change identified.

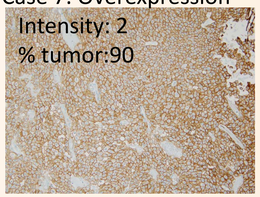
FISH

Expressed as percent cases positive for gene amplification.

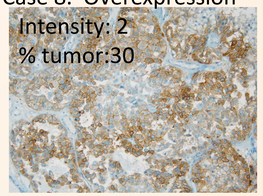
Biomarker	# +	# -	%
cMET	0	2	0%
EGFR	0	9	0%
HER2	0	5	0%
TOPO2A	0	2	0%

cKIT expression by IHC

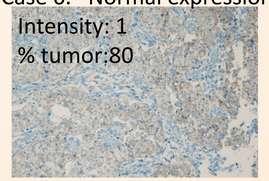
Case 7. Overexpression



Case 8. Overexpression

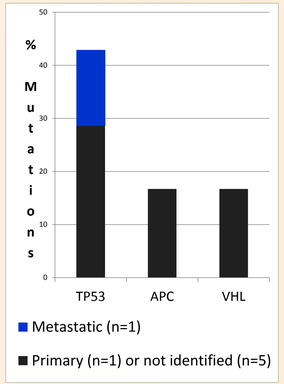


Case 6. Normal expression



Gene sequencing of tumor DNA

NGS revealed mutations in 3 genes in 3 of 7 evaluable tumors. Two *TP53* frameshift mutations (E294fs and T319fs) were identified in one metastatic case (#4). A second case (#6), with noted sarcomatoid features, harbored *TP53* A86fs and also had mutant *APC* (E1317Q), while the third case (#12), with noted sarcomatoid features, had both *TP53* mutation (M340fs) and VHL mutation (E186K).



Genes with no alterations identified included ABL1, AKT1, ALK, ATM, BRAF, BRCA1, BRCA2, CDH1, c-KIT, cMET, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, FBXW7, FGFR1, FGFR2, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, JAK2, JAK3, KDR, KRAS, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMARCB1, SMO, and STK11.

Conclusions

- chRCC has few alterations in “traditional” tumor suppressors and oncogenes. TCGA analysis of chRCC revealed that only *TP53* was mutated at >10% of primary tumors tested (32%).
- Advanced chRCC might be amenable to chemotherapy with 5-fluorouracil, gemcitabine, or temozolamide because of absent TS, RRM1, and MGMT expression, respectively.
- Sunitinib or imatinib but not sorafenib might be preferred tyrosine kinase inhibitors, as cKIT, but not PDGFR, aberrations were detected.

References

Davis CF et al. ‘The Somatic Genomic Landscape of Chromophobe Renal Cell Carcinoma’, *Cancer Cell* 2014, 26, 319–330,