

MTAP loss in sarcomatoid renal cell carcinoma (srcRCC): A genomic landscape study.

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Background: srcRCC is a rare, highly aggressive malignancy with poor prognosis, and thus further exploration of genomic profiling is essential in development of the targeted therapies. Recent evidence has emerged that novel anti-cancer treatments focused on synthetic lethality mechanisms may have efficacy in patients with clinically advanced malignancies. **Methods:** Using the FoundationOne CDx assay, 140 srcRCC underwent hybrid capture based comprehensive genomic profiling (CGP) to identify all classes of genomic alterations (GA). Micro-satellite instability status (MSI) and tumor mutation burden (TMB) were determined from the sequencing data. PD-L1 expression was determined by immunohistochemistry (IHC) using the Dako TPS score (0% = negative; 1-49% = low positive and > 50% = high positive). **Results:** 36 (25.7%) of srcRCC featured whole or partial loss (homozygous deletion) of the MTAP gene. Of the 36 srcRCC with MTAP loss (MTAPloss+) there were 24 (66.7%) cases with 8/8 MTAP exons lost, 1 (2.8%) with 7/8 MTAP exons lost, 1 (2.8%) 6/8 MTAP exons lost, 5 (13.9%) with 4/8 MTAP exons lost and 5 (13.9%) with 3/8 MTAP exons lost. The srcRCC with MTAPloss+ were younger (median age of 60 vs 63 years; $p < .0001$) and more often male gender (75.0% vs 72.1%; NS), compared to MTAP wild type (MTAPloss-). Biomarkers of immunotherapy response in MTAPloss+ vs MTAPloss- srcRCC including MSI High status (2.8% vs 1.0%) and TMB 10-20 mutations/Mb (2.8% vs 3.8%; NS) were uncommon in both groups. At least 1% or higher PD-L1 expression was also similarly high in both groups (75.0% vs 71.4%; NS) in both groups. CDKN2A (100.0% vs 28.4%; $p < .0001$) and CDKN2B (97.2% vs 23.1%; $p < .0001$) were co-deleted with MTAP in the MTAPloss+ srcRCC. Other GA more frequent in the MTAPloss+ AM groups included NF2 (38.9% vs 20.2%; NS) and TERT (30.6% vs 18.3%; NS). GA more frequent in the MTAPloss- srcRCC included RB1 (13.5% vs 0.0%; NS), and TP53 (16.7% vs 40.4%; NS). GA in the VHL gene were similar in both groups (44.4% vs 41.3%; NS). **Conclusions:** MTAP loss+ status occurs in 25.7% of srcRCC and is most often associated with loss of all 8 exons (66.7%) of the MTAP gene. Although the biomarkers associated with immunotherapy response (MSI, TMB, PD-L1) are similar in both groups, the genomic landscape of MTAPloss+ srcRCC is different from that in MTAPloss- srcRCC. Further study of MTAPloss+ srcRCC in the emerging era of PRMT5 and MAT2A inhibitor-based clinical development appears warranted. Research Sponsor: None.

	MTAP Loss 36 cases	MTAP Wild Type 104 cases	P value
CDKN2A	100.0%	32.7%	<.0001
CDKN2B	97.2%	23.1%	<.0001
NF2	38.9%	20.2%	0.20
RB1	0.0%	13.5%	0.12
TERT	30.6%	18.3%	0.38
TP53	16.7%	40.4%	0.09
VHL	44.4%	41.3%	1.0