Molecular analysis of archival clear cell sarcoma tissue samples from EORTC trial 90101 "CREATE" and correlation with response to crizotinib

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Background

- Approximately 90% of clear cell sarcomas (CCSA) harbor an Ewing sarcoma breakpoint region 1 (*EWSR1*) rearrangement resulting in aberrant transcription of multiple genes including MET receptor tyrosine kinase
- EORTC 90101 "CREATE" evaluated the MET inhibitor crizotinib in CCSA but was associated with a low rate of objective responses
- We used archival tumor material from CREATE patients to detect additional molecular alterations and correlate them with clinical features

Material and methods

- DNA from archival CCSA material (primary tumors or metastatic lesions) collected from 24 patients was sequenced using Illumina HiSeq 4000
- Low coverage whole genome sequencing and genomic identification of significant targets in cancer (GISTIC) were performed to detect copy number alterations (CNAs)
- Whole exome sequencing (WES), Genome Analysis ToolKit and Dindel were used to assess the mutational landscape
- Kaplan-Meier estimates were used to determine the association between detected molecular alterations and clinical outcomes

Results

We detected CNAs in all CCSA cases. Significant copy number gains (red) and losses (blue) on chromosomal arm (Fig. 1A) and region (Fig. 1B) levels, detected by GISTIC were plotted (significance threshold q-value <0.25). Cancer consensus genes (CCGs, genes contain alterations which have been causally implicated in cancer and been catalogued by COSMIC cancer database) affected by CNAs were indicated in orange. Kaplan-Meier estimates were used to reveal that loss of chromosome 9q (Fig. 1C) and 12q24.33 (Fig. 1D) were associated with poor overall survival (OS) and progression free survival (PFS) in CCSA patients, respectively.

Fig. 1A

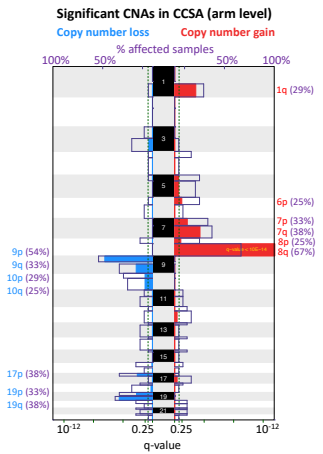


Fig. 1B

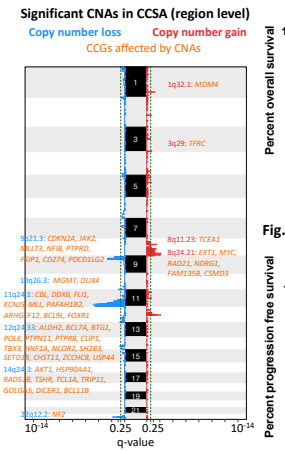


Fig. 1C

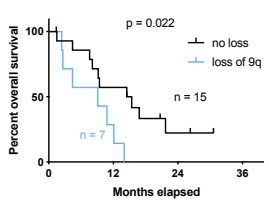
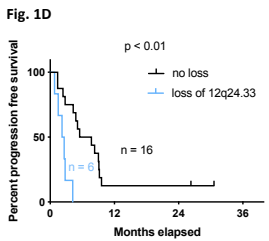


Fig. 1D



The mutational profile of CCSA was assessed and described. CCGs altered by damaging mutations (predicted by PolyPhen-2) in at least 2 of 24 CCSAs were present in Fig. 2A. Mutations in *NIN* and *UBR5* were found to be associated with poor OS and PFS in 22 assessible CCSA patients (Fig. 2B). *UBR5* could target specific proteins for ubiquitin-mediated proteolysis and was found disrupted in many cancers. *NIN* was found to play an important role for centrosomal function.

Fig. 2A

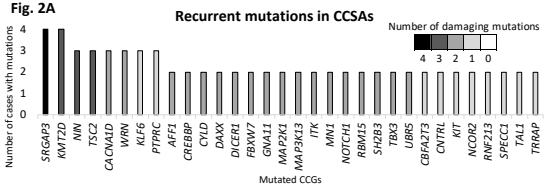
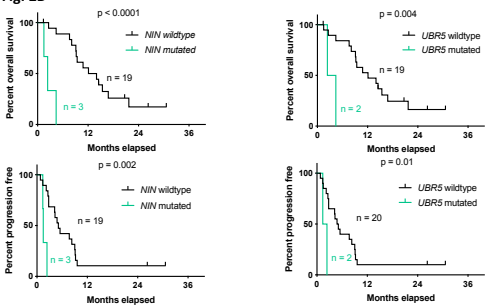
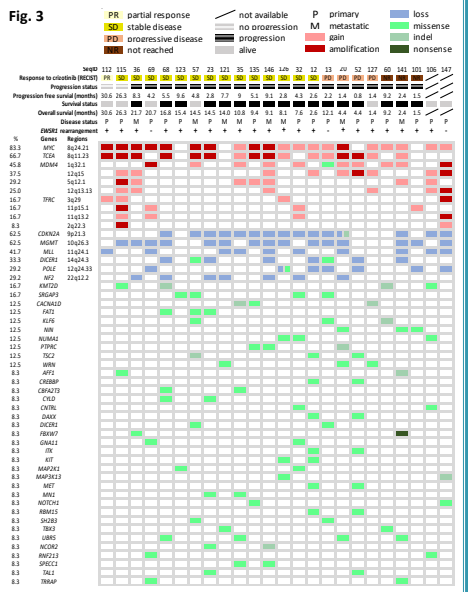


Fig. 2B



Gene alteration landscape in 24 CCSAs (Fig. 3). Affected regions and genes were ranked according to their frequencies of alterations.

Fig. 3



Conclusion

We identified a number of molecular alterations in archival CCSAs and provide further insight into the molecular profile of this ultra-rare malignancy, which may potentially lead to the identification of novel targets and treatment approaches. Recently, we joined forces with teams from Portland and Essen to compile data from more CCSA cases and perform even more comprehensive analysis of the molecular landscape with transcriptome sequencing.

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